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(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel
secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so
produced.



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POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

RELATED APPLICATIONS

- This application claims the benefit of prior-filed provisional patent application
- 5 U.S. Serial No. 60/195,605 entitled "Polynucleotides encoding Novel Secreted Proteins", filed April 6, 2000. The content of the above-referenced application is incorporated in its entirety.

FIELD OF THE INVENTION

- 10 The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

- 15 Gargantuan efforts have been employed by various investigational projects to randomly sequence portions of naturally-occurring cDNAs. The rationale behind this approach to identification and sequencing genes is founded in two basic principles: (1) that transcribed cDNAs represent the product of the most important genes, namely those that are actually expressed *in vivo*, and (2) that efforts to sequence genes and
- 20 other portions of the genome of target organisms which are not actually expressed wastes substantial effort on areas not likely to yield genetic information of therapeutic importance. Thus, the high-throughput sequencing efforts focus on only those portions of the genome which are expressed. The randomly produced cDNA sequences represent "expressed sequence tags" or "ESTs", which identify and can be used as
- 25 probes for the longer, full-length cDNA or genomic sequence from which they were transcribed.

- Although this "shortcut" approach to genomic sequencing presents savings of effort compared to sequencing of the complete genome, it still produced a vast array of ESTs which may not be directly useful as protein therapeutics. To date, the majority of
- 30 protein-related drug discovery has focused on the use of secreted proteins to produce a desired therapeutic effect. Since the EST approach theoretically identifies all expressed proteins, it produces an EST library which contains a mixture of secreted proteins (such as hormones, cytokines and receptors) and non-secreted proteins (such as, for example, metabolic enzymes and cellular structural proteins), without identifying which ESTs
- 35 correspond to proteins falling into either category. As a result, these methods are not optimally tailored to the needs of investigators searching for secreted proteins because

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they must separate the secreted "wheat" from the non-secreted "chaff", wasting effort and resources in the process.

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the
5 past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning).

10 More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to
15 have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. Co-assigned U.S. Patent No. 5,536,637, which is incorporated herein by reference, provides methods for focusing genomic sequencing efforts on sequences encoding the secreted proteins which are of most interest for identification of protein therapeutics.
20 The '637 patent discloses a "signal sequence trap" which selectively identifies partial sequences encoding secreted proteins, namely "secreted expressed sequence tags" or "sESTs". The sequences of these sESTs can be used to design probes to isolate the full-length cDNA clones that encode secreted proteins.

It is to these secreted proteins and the full-length polynucleotides encoding
25 them that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention provides for full-length cDNAs isolated from a variety of human RNA/cDNA sources which encode novel secreted proteins.

30 In preferred embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:
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20 NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623;
or a complement of said sequence.

In other embodiments, the present invention provides an isolated
polynucleotide consisting of a nucleotide sequence selected from the group consisting
of:

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- 5 In further embodiments, the present invention provides an isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of:

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NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623;

or a complement of said sequence.

30 In yet other embodiments, the present invention provides an isolated
polynucleotide comprising a nucleotide sequence which hybridizes to a sequence
selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID
NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID
35 NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID
NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID
NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID

NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID
NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID
NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID
NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID
5 NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID
NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID
NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID
NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID
NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID
10 NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID
NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID
NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID
NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID
NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID
15 NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID
NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ
ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110,
SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID
NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ
20 ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124,
SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID
NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ
ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138,
SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID
25 NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ
ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152,
SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID
NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ
ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166,
30 SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID
NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ
ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180,
SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID
NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ
35 ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194,
SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID
NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ

ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208,
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ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222,
5 SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID
NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ
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20 SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID
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35 SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID
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10 SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID
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NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, and SEQ ID NO:623; or to a complement of said sequence.

The invention also provides for proteins encoded by the above-described polynucleotides. In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

- Processes are also provided for producing a protein, which comprise:
- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
 - (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention,

and/or a polynucleotide of the present invention, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

- 5 The nucleotide sequences of the isolated cDNAs of the present invention are reported in the Sequence Listing below. Table 2 lists the "Clone ID Nos." assigned by applicants to each SEQ ID NO: in the Sequence Listing.

Table 2

- 10 Each pair of entries in this table consists of the SEQ ID NO (e.g., 1, 2, etc.) followed by the Clone ID No. for such sequence (e.g., AA351_2, AA351_6, etc.).

1	AA351_2	201	MR315_1w	401	YB104_1	601	YCA1_1
2	AA351_6	202	NA1142_2	402	YB105_1	602	YCA2_1
3	AA36_21	203	NB31_13s	403	YB106_1	603	YCA3_1
4	AC423_6	204	NF61_3	404	YB107_1	604	YCA4_1
5	AJ180_4	205	NH369_4	405	YB108_1	605	YD100_1
6	AJ180_5	206	NH455_6	406	YB109_1	606	YD101_1
7	AJ1_1	207	NM190_1	407	YB10_1	607	YD102_1
8	AJ53_4	208	NN131_1	408	YB110_1	608	YD104_1
9	AK296_1is	209	NN93_1	409	YB111_1	609	YD105_1
10	AM1017_21	210	NN93_5	410	YB112_1	610	YD106_1
11	AM1083_14	211	NS121_9	411	YB113_1	611	YD108_1
12	AM224_1	212	NU232_3	412	YB114_1	612	YD110_1
13	AM340_11	213	NZ149_4	413	YB115_1	613	YD111_1
14	AM931_1is	214	O117_1	414	YB116_1	614	YD112_1
15	AP224_2s	215	OL1_1x	415	YB118_1	615	YD113_1
16	AP226_21	216	OM1_1x	416	YB119_1	616	YD114_1
17	AP259_1w	217	ON1_1x	417	YB120_1	617	YD115_1
18	AR325_2	218	ON2_1x	418	YB121_1	618	YD116_1
19	AR399_3	219	ON3_1x	419	YB122_1	619	YD117_1
20	AR440_1	220	OP1_1x	420	YB123_1	620	YD118_1
21	AS180_1	221	OR1_1	421	YB126_1	621	YD119_1
22	AS23_1	222	OR2_1	422	YB127_1	622	YD11_1
23	AS63_26	223	OR4_1	423	YB128_1	623	YD120_1
24	AS63_29	224	OR5_1	424	YB129_1		
25	AT211_1	225	OR6_1	425	YB130_1		

26	AT211_17	226	OS1_1	426	YB131_1
27	AT340_23	227	PE246_4	427	YB132_1
28	AU106_1	228	PE567_1	428	YB133_1
29	AU107_1	229	PG284_1	429	YB134_1
30	AU118_1	230	PI13_1	430	YB135_1
31	AW92_1	231	PI13_10	431	YB136_1
32	AW92_1s	232	PI13_5	432	YB137_1
33	AX17_1	233	PI198_3	433	YB138_1
34	AX34_1	234	PJ11_2	434	YB140_1
35	AX34_3	235	PJ142_10	435	YB141_1
36	B224_1	236	PJ299_3	436	YB142_1
37	BA91_3	237	PK103_10	437	YB143_1
38	BD176_3	238	PK175_1	438	YB144_1
39	BD316_2	239	PK185_37	439	YB146_1
40	BD486_3	240	PK198_8	440	YB147_1
41	BD579_1w	241	PK224_1	441	YB148_1
42	BF245_1	242	PK224_11	442	YB149_1
43	BG219_2	243	PK224_12	443	YB14_1
44	BG241_1	244	PK224_9	444	YB151_1
45	BG457_1	245	PK259_5	445	YB152_1
46	BG72_1	246	PK266_4s	446	YB153_1
47	BI165_12	247	PK405_1	447	YB154_1
48	BK518_1w	248	PK558_1	448	YB155_1
49	BL196_22	249	PK65_1	449	YB156_1
50	BL229_22	250	PL16_12	450	YB157_1
51	BL249_18	251	PL211_2	451	YB158_1
52	BL255_1	252	PL251_1	452	YB159_1
53	BM41_3s	253	PL33_4	453	YB160_1
54	BN189_1	254	PL360_9	454	YB161_1
55	BN189_18	255	PL501_5	455	YB162_1
56	BO432_1	256	PL566_1s	456	YB163_1
57	BO432_4	257	PL772_2	457	YB165_1
58	BO538_2	258	PL85_3	458	YB166_1
59	BO549_1	259	PM303_10	459	YB167_1
60	BO71_1	260	PM347_4s	460	YB168_1
61	BP175_3	261	PM362_2	461	YB169_1
62	BP813_3	262	PM385_6	462	YB16_1

63	BR595_4	263	PM404_2	463	YB170_1
64	BR595_5	264	PM430_3	464	YB171_1
65	BS81_2	265	PM4_13s	465	YB172_1
66	BS81_2s	266	PM696_10	466	YB173_1
67	BV239_3	267	PP173_1	467	YB174_1
68	BV286_1	268	PP297_2	468	YB175_1
69	BV369_1w	269	PP314_19	469	YB176_1
70	BV370_1w	270	PP345_3	470	YB177_1
71	BV51_1	271	PP411_1	471	YB178_1
72	BZ16_3	272	PP509_3	472	YB17_1
73	BZ16_7	273	PT11_8	473	YB180_1
74	BZ53_1	274	PT215_3s	474	YB181_1
75	BZ644_34	275	PT217_3	475	YB182_1
76	CA106_19xs	276	PT285_20	476	YB184_1
77	CB98_4s	277	PT301_6	477	YB185_1
78	CC194_4	278	PT330_14	478	YB186_1s
79	CC288_9	279	PT35_11	479	YB188_1
80	CC346_1	280	PT364_2	480	YB189_1
81	CC403_3	281	PU234_2	481	YB18_1
82	CC412_1w	282	PU26_1	482	YB190_1
83	CC413_1w	283	PU26_3	483	YB191_1
84	CG158_1	284	PV138_2	484	YB194_1
85	CG432_1	285	PV323_2	485	YB195_1
86	CG432_2	286	PV549_2	486	YB198_1
87	CG432_3	287	PW102_9	487	YB199_1
88	CI247_3	288	PW123_7	488	YB1_1
89	CJ24_10	289	PW214_15s	489	YB200_1
90	CJ397_1	290	PW245_1	490	YB201_1
91	CJ84_3	291	PW328_4	491	YB202_1
92	CN1004_1w	292	PW378_2	492	YB203_1
93	CN173_1	293	PW429_13	493	YB205_1
94	CN238_1s	294	PW447_2	494	YB206_1
95	CO1256_1w	295	PW471_2	495	YB207_1
96	CO71_1	296	PX202_14	496	YB208_1
97	CO908_1	297	Q691_4x	497	YB209_1
98	CO908_41	298	QB216_2	498	YB20_1
99	CR1155_1	299	QB282_1	499	YB210_1

100	CR491_1	300	QC337_1	500	YB211_1
101	CT636_1	301	QC488_1	501	YB212_1
102	CT702_8	302	QC525_1	502	YB213_1
103	CW675_3	303	QF17_1	503	YB214_1
104	CW691_11s	304	QF241_1	504	YB216_1
105	CZ770_1	305	QF2_1	505	YB217_1
106	CZ770_7	306	QF320_1	506	YB218_1
107	D329_1	307	QF464_7	507	YB220_1
108	D68_2	308	QG373_2	508	YB221_1
109	DA136_11	309	QG537_4	509	YB223_1
110	DA136_33	310	QG591_2	510	YB224_1
111	DA348_5	311	QM22_2	511	YB225_1
112	DA451_1	312	QU332_1	512	YB227_1
113	DA451_2	313	QV257_1	513	YB229_1
114	DD352_1	314	QV326_3	514	YB230_1
115	DD413_3	315	QV349_4	515	YB231_1
116	DE121_1w	316	QV378_2	516	YB232_1
117	DE122_1w	317	QX338_20	517	YB234_1
118	DF780_11	318	QY1263_1	518	YB236_1
119	DF835_1	319	QY1352_1	519	YB237_1
120	DH1349_1	320	QY1756_4	520	YB238_1
121	DH1361_1w	321	QY356_1	521	YB241_1
122	DI362_3	322	QY385_10	522	YB242_1
123	DI366_3	323	RA726_2	523	YB243_1
124	DI448_11	324	RB342_3	524	YB244_1
125	DK230_12	325	RB535_1	525	YB245_1
126	DK329_16	326	RB771_6	526	YB246_1
127	DK70_15	327	RB778_5	527	YB248_1
128	DN153_8	328	RB792_14	528	YB254_1
129	DN714_2	329	RD1058_2	529	YB260_1
130	DN721_8s	330	RD1111_2	530	YB261_1
131	DN732_1	331	RD207_1	531	YB27_1
132	DU160_15	332	RD309_2	532	YB32_1
133	DU238_1	333	RD616_11	533	YB41_1
134	DU238_1s	334	RD62_4	534	YB45_1
135	DU416_1	335	RD959_3	535	YB46_1
136	DU416_11	336	RG452_1	536	YB48_1

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137	DU416_2	337	RG661_1	537	YB4_1
138	DW1013_1w	338	RJ118_2	538	YB50_1
139	DX153_7	339	RJ402_4	539	YB52_1
140	EC428_2	340	RJ7_1	540	YB53_1
141	EE242_1w	341	RJ898_1	541	YB55_1
142	EH12_12	342	RJ900_18	542	YB59_1
143	EI16_13	343	WA153_2	543	YB61_1
144	EI16_13s	344	WA545_8	544	YB65_1
145	EI250_1	345	WA628_2	545	YB67_1
146	EJ254_1	346	WA628_5	546	YB68_1
147	EL15_14	347	WG67_19	547	YB6_1
148	EM446_1w	348	YD121_1	548	YB75_1
149	EN256_11	349	YD122_1	549	YB75_11
150	EN37_1	350	YA18_1	550	YB78_1
151	ET84_1	351	YA25_1	551	YB83_1
152	EZ265_1w	352	YA26_1	552	YB86_1
153	FG372_41	353	YA30_1	553	YB87_1
154	FG966_1w	354	YA31_1	554	YB92_1
155	FH6_12	355	YA33_1	555	YB93_1
156	FJ283_11s	356	YA34_1	556	YB94_1
157	FS185_1w	357	YA36_1	557	YB95_1
158	FX127_21	358	YA37_1	558	YB96_1
159	FX541_1w	359	YA39_1	559	YB97_1
160	FY356_14	360	YA3_1	560	YB98_1
161	FY641_1w	361	YA40_1	561	YB99_1
162	FZ87_2	362	YA45_1	562	YB9_1
163	G55_1	363	YA46_1	563	YBA1_1
164	GE553_1w	364	YA47_1	564	YBA2_1
165	GE554_1w	365	YA48_1	565	YC12_1
166	GX619_8	366	YA50_1	566	YC16_1
167	GX760_23	367	YA51_1	567	YC1_1
168	GY622_1w	368	YA52_1	568	YC21_1
169	H298_23	369	YA53_1	569	YC22_1
170	H541_3is	370	YA55_1	570	YC30_1
171	HC986_1	371	YA56_1	571	YC31_1
172	HZ162_4	372	YA57_1	572	YC32_1
173	IG35_12	373	YA58_1	573	YC33_1

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174	IJ1442_3	374	YA59_1	574	YC35_1
175	IK644_1w	375	YA5_1	575	YC36_1
176	IS114_1	376	YA60_1	576	YC37_1
177	J143_1	377	YA61_1	577	YC38_1
178	J218_15	378	YA62_1	578	YC39_1
179	K289_4	379	YA63_1	579	YC3_1
180	K421_1x	380	YA64_1	580	YC41_1
181	K446_3	381	YA68_1	581	YC42_1
182	K511_1is	382	YA71_1	582	YC43_1
183	KJ921_1w	383	YA72_1	583	YC44_1
184	KM14_4	384	YA73_1	584	YC45_1
185	KZ316_1w	385	YA74_1	585	YC46_1
186	LF307_5	386	YA76_1	586	YC47_1
187	LR607_12	387	YA78_1	587	YC50_1
188	LT390_9	388	YA79_1	588	YC51_1
189	LT403_2	389	YA81_1	589	YC52_1
190	LT706_1w	390	YA82_1	590	YC54_1
191	LU524_2	391	YA83_1	591	YC55_1
192	M141_1	392	YA84_1	592	YC56_1
193	MA278_1w	393	YA85_1	593	YC57_1
194	MD312_1	394	YA8_1	594	YC58_1
195	ME514_7	395	YAA1_1	595	YC59_1
196	ME796_1	396	YAA2_1	596	YC5_1
197	ML227_1	397	YAA3_1	597	YC61_1
198	MM197_1	398	YB100_1	598	YC62_1
199	MM367_6	399	YB102_1	599	YC63_1
200	MN341_2	400	YB103_1	600	YC64_1

The "Clone ID No." for a particular clone consists of one or two letters followed by a number. The letters designate the tissue source from which the sEST for that clone was initially isolated. Table 3 below lists the various sources which were run through applicants' signal sequence trap.

TABLE 3

Sel.	Species	Stage	Tissue	Cell Type	Treatment
AA	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
AC	Human	Fetal	Placenta	26yrs., 1 specimen	None
5 AJ	Human	Adult	Testes	10-61yrs., pool of 11	None
AK	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
AM	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
AP	Human	Fetal	Placenta	26yrs., 1 specimen	None
AR	Human	Adult	Retina	16-75yrs., pool of 76	None
10 AS	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
AT	Human	Adult	Blood	Lymphocytes+Dendritic Cells	MLR
AU	Human	Adult	Testes	10-61yrs., pool of 11	None
AW	Human	Adult	Ovary	PA-1 Teratocarcinoma line	RA+activin
AX	Human	Adult	Testes	10-61yrs., pool of 11	None
15 B	Human	Adult	Blood	PBMC	ConA + PMA
BA	Human	Fetal	Placenta	26yrs., 1 specimen	None
BD	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
BF	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
BG	Human	Adult	Brain	N/A	None
20 BI	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
BK	Human	Adult	Retina	16-75yrs., pool of 76	None
BL	Human	Adult	Testes	10-61yrs., pool of 11	None
BM	Human	Adult	Muscle	N/A	None
BN	Human	Fetal	Placenta	26yrs., 1 specimen	None
25 BO	Human	Adult	Retina	16-75yrs., pool of 76	None
BP	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
BR	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
BS	Human	Adult	Pituitary	N/A	None
BV	Human	Adult	Brain	N/A	None
30 BZ	Human	Fetal	Kidney	19-23wks., M/F pool of 5	None
CA	Mouse	Fetal	Embryo	ES line embryoid bodies	2-12d post LIF
CB	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
CC	Human	Adult	Brain	N/A	None
CG	Human	Adult	Testes	10-61yrs., pool of 11	None
35 CI	Human	Adult	Brain	N/A	None
CJ	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
CN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
CO	Human	Adult	Brain	N/A	None
CR	Human	Adult	Testes	10-61yrs., pool of 11	None
40 CT	Human	Adult	Brain	N/A	None
CW	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
CZ	Human	Adult	Testes	10-61yrs., pool of 11	None
D	Human	Adult	Blood	PBMC	ConA + PMA
DA	Human	Fetal	Placenta	26yrs., 1 specimen	None
45 DD	Human	Adult	Testes	10-61yrs., pool of 11	None
DE	Human	Adult	Testes	Teratocarcinoma NCCIT line	None

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	DF	Human	Adult	Brain	N/A	None
	DH	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DI	Human	Adult	Testes	10-61yrs., pool of 11	None
	DK	Human	Fetal	Kidney	N/A	None
5	DN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DU	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	DW	Human	Adult	Brain	N/A	None
	DX	Human	Adult	Testes	10-61yrs., pool of 11	None
	EC	Human	Adult	Brain	N/A	None
10	EE	Human	Adult	Testes	10-61yrs., pool of 11	None
	EH	Human	Adult	Blood	PBMC	G-CSF in vivo
	EI	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	EJ	Human	Fetal	Placenta	26yrs., 1 specimen	None
	EL	Human	Adult	Testes	10-61yrs., pool of 11	None
15	EM	Human	Fetal	Kidney	N/A	None
	EN	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	ET	Human	Adult	Testes	10-61yrs., pool of 11	None
	EZ	Human	Fetal	Kidney	N/A	None
	FG	Human	Adult	Brain	N/A	None
20	FH	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	FJ	Human	Adult	Lung	Carcinoma line	None
	FS	Human	Adult	Testes	10-61yrs., pool of 11	None
	FX	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	FY	Human	Fetal	Placenta	26yrs., 1 specimen	None
25	FZ	Human	Fetal	Placenta	26yrs., 1 specimen	None
	G	Human	Adult	Blood	PBMC	ConA + PMA
	GE	Human	Adult	Brain	N/A	None
	GX	Human	Adult	Brain	N/A	None
	GY	Human	Adult	Testes	10-61yrs., pool of 11	None
30	H	Human	Adult	Blood	PBMC	PHA+PMA+MLR
	HC	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	HZ	Human	Adult	Brain	Thalamus	None
	IG	Human	Adult	Testes	10-61yrs., pool of 11	None
	IJ	Human	Adult	Blood	PBMC	G-CSF in vivo
35	IK	Human	Adult	Retina	Retinoblastoma Y79 line	None
	IS	Human	Adult	Trachea	N/A	None
	J	Human	Adult	Blood	PBMC	PHA+PMA+MLR
	K	Mouse	Adult	Bone Marrow	Stromal line FCM-4	None
	KJ	Human	Fetal	Brain	N/A	None
40	KM	Human	Adult	Retina	Retinoblastoma Y79 line	None
	KZ	Human	Adult	Retina	16-75yrs., pool of 76	None
	LF	Human	Adult	Spinal Cord	N/A	None
	LR	Human	Adult	Lymph Node	N/A	None
	LT	Human	Adult	Retina	Retinoblastoma Y79 line	None
45	LU	Human	Adult	Retina	Retinoblastoma Y79 line	None
	M	Human	Adult	Neural	Glioblastoma line T98G	None

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	MA	Human	Fetal	Carcinoma	NTD2-1 line	None
	MD	Human	Fetal	Kidney	N/A	None
	ME	Human	Adult	Brain	Substantia Nigra	None
	ML	Human	Adult	Brain	Caudate Nucleus	None
5	MM	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
	MN	Human	Adult	Brain	Hippocampus	None
	MR	Human	Adult	Testes	N/A	None
	NA	Human	Adult	Brain	Corpus Callosum	None
	NB	Human	Adult	Spinal Cord	N/A	None
10	NF	Human	Adult	Brain	Substantia Nigra	None
	NH	Human	Adult	Brain	Thalamus	None
	NM	Human	Adult	Blood	Erythroleukemia TF-1 line	None
	NN	Human	Adult	Kidney	293 embryonal carcinoma line	None
	NS	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
15	NU	Human	Adult	Brain	Caudate Nucleus	None
	NZ	Human	Adult	Blood	Erythroleukemia TF-1 line	None
	O	Human	Adult	Blood	Dendritic Cells	None
	OL	Mouse	Adult	Lymphocyte	Pro-B line FLEB14	None
	OM	Mouse	Adult	Brain	Glioma line T98G	IL-1
20	ON	Mouse	Adult	Brain	Glioma line T98G	IL-1
	OP	Mouse	Adult	Brain	Glioma line T98G	IL-1
	OR	Human	Adult	Brain	Glioma line T98G	IL-1
	OS	Human	Fetal	UC	Endothelial line HUV-EC-C	None
	PE	Human	Adult	Blood	K562 chronic ML line	None
25	PG	Human	Adult	Thyroid	N/A	None
	PI	Human	Adult	Thyroid	N/A	None
	PJ	Human	Adult	Testes	EC NT2D1 line	RA for 23 days
	PK	Human	Adult	Kidney	293 embryonal carcinoma line	None
	PL	Human	Adult	Kidney	293 embryonal carcinoma line	None
30	PM	Human	Adult	Kidney	293 embryonal carcinoma line	None
	PP	Human	Adult	Blood	LL MOLT-4 line	None
	PT	Human	Adult	Blood	LL MOLT-4 line	None
	PU	Human	Adult	Blood	PL HL-60 line	None
	PV	Human	Adult	Brain	Cerebellum	None
35	PW	Human	Adult	Brain	Cerebellum	None
	PX	Human	Adult	Brain	Cerebellum	None
	Q	Mouse	Adult	Bone Marrow	N/A	5 fluoro-uracil
	QB	Human	Adult	Bladder	5637 carcinoma line	None
	QC	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
40	QF	Human	Adult	Bladder	5637 carcinoma line	None
	QG	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
	QM	Human	Adult	Blood	Histiocytic lymphoma U937 line	None
	QU	Human	Adult	Blood	K562 chronic ML line	None
	QV	Human	Adult	Testes	EC NT2D1 line	RA for 23 days
45	QX	Human	Adult	Bone	RD-ES line	None
	QY	Human	Adult	Blood	PL HL-60 line	None

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	RA	Human	Adult	Brain	Substantia Nigra	None
	RB	Human	Adult	Kidney	293 embryonal carcinoma line	None
	RD	Human	Adult	Kidney	293 embryonal carcinoma line	None
	RG	Human	Adult	Blood	PL HL-60 line	None
5	RJ	Human	Adult	Neural	Neuroepithelioma HTB-10 line	None
	WA	Xenopus	Fetal	Embryo	Dorsal Mesoderm	None
	WG	Xenopus	Fetal	Embryo	Dorsal Mesoderm	None
	YA	Human	Adult	Testes	10-61yrs., pool of 11	None
	YAA	Human	Adult	Bone	Osteosarcoma MG63 line	None
10	YB	Human	Fetal	Brain	19-23wks., M/F pool of 5	None
	YBA	Human	Adult	Lymph Node	N/A	None
	YC	Human	Adult	Kidney	293 embryonal carcinoma line	None
	YCA	Human	Adult	Thymus	N/A	None
	YD	Human	Adult	Brain	N/A	None

15

Table 3 Cell Type and Treatment Key:

	2-12d post LIF:	2-12 days after LIF removal
	ConA:	concanavalin A
	EC:	Embryonal Carcinoma
20	G-CSF:	granulocyte-colony stimulating factor
	LL:	Lymphoblastic Leukemia
	ML:	myelogenous leukemia
	MLR:	mixed lymphocyte reaction
	PHA:	phytohemagglutinin
25	PL:	Promyelocytic Leukemia
	PMA:	phorbol myristate acetate
	PMBC:	peripheral blood mononuclear cells
	RA:	retinoic acid
	RA+activin:	Pool of RA-treated + activin-treated + untreated tissue
30	UC:	Umbilical Cord

Thus, the tissue source for a particular sEST sequence can be identified in Table 3 by the one and two letter designations used in the relevant "Clone ID No." in Table 2. For example, a sEST designated as "PP85" would have been isolated from a human adult blood (lymphoblastic leukemia MOLT-4) library (i.e., selection "PF") as indicated in Table 3. These sEST sequences were then used to isolate the full-length cDNA clones listed in Table 2; these full-length cDNA clones are generally human cDNA clones as described in the Sequence Listing appended hereto.

As used herein, "polynucleotide" includes single- and double-stranded RNAs, DNAs and RNA:DNA hybrids.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention.

10 Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, *Bio/Technology* 10, 773-778 (1992) and in R.S. McDowell, *et al.*, *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the

15 valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

20 The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable

25 mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are

30 derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence

35 information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic

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materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

- The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can then be performed at an Internet site provided by the National Center for Biotechnology Information having the address www.ncbi.nlm.nih.gov/UniGene, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

- Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250- 254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et*

al., 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* 266: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* 215: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* 3: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in

molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from the Internet file-transfer protocol (FTP) site <ftp://blast.wustl.edu/blast/executables>. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated

from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*,
 5 *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species
 10 (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682- 690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

15 The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at
 20 least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from
 25 individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most
 30 preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M- R.

35

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [†]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T _B [*] ; 1xSSC	T _B [*] ; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T _D [*] ; 1xSSC	T _D [*] ; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T _F [*] ; 1xSSC	T _F [*] ; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T _H [*] ; 4xSSC	T _H [*] ; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T _J [*] ; 4xSSC	T _J [*] ; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T _L [*] ; 2xSSC	T _L [*] ; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T _N [*] ; 6xSSC	T _N [*] ; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T _P [*] ; 6xSSC	T _P [*] ; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T _R [*] ; 4xSSC	T _R [*] ; 4xSSC

[†]: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et

al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may contain sequences at its 5' and/or 3' end that are derived from linker, polylinker, or multiple cloning site sequences commonly found in vectors such as the pMT2 or pED expression vectors (see below). For example, sequences such as SEQ ID NO:626, SEQ ID NO:627, or SEQ ID NO:628 may be found at the 5' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 3' end. Similarly, sequences such as SEQ ID NO:629, SEQ ID NO:630, or SEQ ID NO:631 may be found at the 3' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 5' end. In addition, variants of these linker sequences may be present in isolated polynucleotides of the invention, which linker variants vary from SEQ ID NO:626 through SEQ ID NO:631 by the alteration, insertion, or deletion of one or more nucleotides. Therefore, a preferred embodiment of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 25 and ending at nucleotide (N-25) of the SEQ ID NO for that polynucleotide, where N represents the total number of nucleotides in the sequence. As a specific example, a preferred embodiment of the invention comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 25 to nucleotide 1616, where the total number of nucleotides (N) in SEQ ID NO:1 is 1641, and N-25 equals 1616. More preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 30 and ending at nucleotide (N-30) of the SEQ ID NO for that polynucleotide. Most preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 35 and ending at nucleotide (N-35) of the SEQ ID NO for that polynucleotide. Similarly, additional embodiments are those nucleotide sequences that extend from nucleotide 40 to nucleotide (N-40), or from nucleotide 45 to nucleotide (N-45), or from nucleotide 50 to nucleotide (N-50), or from nucleotide 60 to nucleotide (N-60), or from nucleotide 65 to

nucleotide (N-65), or from nucleotide 70 to nucleotide (N-70), or from nucleotide 75 to nucleotide (N-75), or from nucleotide 80 to nucleotide (N-80), etc., for any of the polynucleotides disclosed herein. Further preferred embodiments are those nucleotide sequences that are subsequences of the nucleotide sequences disclosed herein,

- 5 beginning at any nucleotide position selected from the group consisting of nucleotide 5, nucleotide 10, nucleotide 15, nucleotide 20, nucleotide 25, nucleotide 30, nucleotide 35, nucleotide 40, nucleotide 45, nucleotide 50, nucleotide 55, nucleotide 60, nucleotide 65, nucleotide 70, nucleotide 75, or nucleotide 80, and ending at any nucleotide position selected from the group consisting of nucleotide (N-5), nucleotide (N-10), nucleotide
10 (N-15), nucleotide (N-20), nucleotide (N-25), nucleotide (N-30), nucleotide (N-35), nucleotide (N-40), nucleotide (N-45), nucleotide (N-50), nucleotide (N-55), nucleotide (N-60), nucleotide (N-65), nucleotide (N-70), nucleotide (N-75), or nucleotide (N-80), wherein N is the total number of nucleotides disclosed for a particular SEQ ID NO.

- The isolated polynucleotide of the invention may be operably linked to an
15 expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined
20 herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

- A number of types of cells may act as suitable host cells for expression of the
25 protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

- 30 Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*,
35 *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the

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appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin- toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

5 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,
10 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

 The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are
15 naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may
20 be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

25 Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

30

USES AND BIOLOGICAL ACTIVITY

 The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the
35 present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The primary use of polynucleotides of the invention which are sESTs is as probes for the identification and isolation of full-length cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide sequence of which substantially the entire sEST is a fragment in the case of a full-length cDNA, or which encodes the sEST in the case of a genomic DNA molecule) to such sESTs. Techniques for use of such sequences as probes for larger cDNAs or genomic molecules are well known in the art.

10 The polynucleotides can also be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify
15 chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers
20 for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the
25 polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to
30 determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a
35 particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand

interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

- 5 Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, 10 Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

- 15 Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a 20 separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

- 25 A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one 30 or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, 35 Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, *Immunologic studies in Humans*); Weinberger et al., *Proc. Natl. Acad. Sci. USA* 77:6091-6095, 1980; Weinberger et al., *Eur. J. Immun.* 11:405-

411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

5 A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B
10 lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including
15 infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present
20 invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment
25 of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses,
30 in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires
35 continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure

to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the

production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-

specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982;

Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

- 5 Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*, J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto.
- 10 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan,

- 15 A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

- 20 Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia et al., *Journal of Immunology* 154:5071-5079, 1995; Porgador et al., *Journal of Experimental Medicine* 182:255-260,
- 25 1995; Nair et al., *Journal of Virology* 67:4062-4069, 1993; Huang et al., *Science* 264:961-965, 1994; Macatonia et al., *Journal of Experimental Medicine* 169:1255-1264, 1989; Bhardwaj et al., *Journal of Clinical Investigation* 94:797-807, 1994; and Inaba et al., *Journal of Experimental Medicine* 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in:

- 30 Darzynkiewicz et al., *Cytometry* 13:795-808, 1992; Gorczyca et al., *Leukemia* 7:659-670, 1993; Gorczyca et al., *Cancer Research* 53:1945-1951, 1993; Itoh et al., *Cell* 66:233-243, 1991; Zacharchuk, *Journal of Immunology* 145:4037-4045, 1990; Zamai et al., *Cytometry*
- 35 14:891-897, 1993; Gorczyca et al., *International Journal of Oncology* 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

5

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A

protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured
5 by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

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Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or
15 endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in
20 improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a
25 population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or
30 prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience
35 (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J.*

Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

- 5 A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or
- 10 inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

- 15 Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

- 20 A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands,
- 25 receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the
- 30 relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

- 35 Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

- Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell
- 5 80:661-670, 1995.

Anti-Inflammatory Activity

- Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells
- 10 involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to
- 15 treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine- induced lung injury, inflammatory bowel disease, Crohn's
- 20 disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

- 25 In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support
- 30 tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

- 35 A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other

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parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

5 caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders),

10 depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as,

15 for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

20 ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier)

25 diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines,

30 or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional

35 factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular

cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

- 5 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

- The pharmaceutical composition of the invention may be in the form of a
10 complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and
15 structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies
20 able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

- The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which
25 exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S.
30 Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

- As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or
35 amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When

applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a
5 therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more
10 cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with
15 cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or
20 cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the
25 pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean
30 oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present
35 invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 μ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at

the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the
5 invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the
10 protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When
15 administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may
20 also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the
25 developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular
30 application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure
35 proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of

the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

5 Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

10 A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include
15 hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so
20 much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue
25 in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

 The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to
30 humans, are desired patients for such treatment with proteins of the present invention.

 The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size
35 of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other

proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

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or a complement of said sequence.

2. An isolated polynucleotide consisting of a nucleotide sequence selected
from the group consisting of:

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3. An isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID

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5 4. The polynucleotide of any one of claims 1-3, wherein said polynucleotide is operably linked to at least one expression control sequence.

 5. A vector comprising the polynucleotide of claim 4.

10 6. A host cell transformed with a vector comprising the polynucleotide of any one of claims 1-3.

 7. A process for producing a protein encoded by the polynucleotide of claim 4, which process comprises:

15 (a) growing a culture of a host cell in a suitable culture medium, wherein the host cell has been transformed with the polynucleotide of claim 4; and
 (b) purifying said protein from the culture.

 8. A protein produced according to the process of claim 7.

20

 9. An antibody that specifically binds to the protein of claim 8.

 10. A method for detecting the protein of claim 8, comprising contacting a sample suspected of containing the protein with an antibody that specifically binds to the protein, under conditions such that the antibody binds the protein and the protein is detected.

 11. A method for detecting the polynucleotide of any one of claims 1-3, comprising contacting a sample suspected of containing the polynucleotide with a polynucleotide reagent that hybridizes to the polynucleotide, under conditions such that the reagent binds the polynucleotide and the polynucleotide is detected.

 12. The method of claim 10 or 11, wherein the sample is a biological sample.

35 13. The method of claim 12, where the biological sample is isolated from a human.

14. A method of identifying a compound that modulates the activity of the protein of claim 8, comprising contacting a composition comprising the protein with a test compound and monitoring the effect of the test compound on the activity of the protein, such that a modulatory compound is identified.

5

15. A method of identifying a compound that modulates the expression of the polynucleotide of any one of claims 1-3, comprising contacting a cell that expresses the polynucleotide with a test compound and determining the effect of the test compound on the expression of the polynucleotide, such that a modulatory compound is identified.

10

16. A method of identifying a compound that modulates the production of the protein of claim 8, comprising contacting a cell that produces the protein with the test compound and determining the effect of the test compound on the production of the protein, such that a modulatory compound is identified.

15

17. A method of treating a subject having a disorder characterized by aberrant expression of the polynucleotide of any one of claims 1-3, comprising administering to said subject a therapeutically effective amount of a compound that modulates expression of the polypeptide, such that treatment is effected.

20

18. A method of treating a subject having a disorder characterized by aberrant production of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates production of the protein, such that treatment is effected.

25

19. A method of treating a subject having a disorder characterized by aberrant activity of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates activity of the protein, such that treatment is effected.

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SEQUENCE LISTING

<110> Jacobs, Kenneth
 McCoy, John M.
 LaVallie, Edward R.
 Collins-Racie, Lisa A.
 Evans, Cheryl
 Merberg, David
 Treacy, Maurice
 Agostino, Michael J.
 Steininger II, Robert J.
 Bowman, Michael R.
 Spaulding, Vikki
 Wong, Gordon G.
 Clark, Hilary
 Pechtcl, Kim
 Howes, Steven H.
 Resnick, Richard J.
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 Genetics Institute, Inc.

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<210> 8

<211> 1337

<212> DNA

<213> Homo sapiens

<400> 8

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<210> 9

<211> 1197

<212> DNA

<213> Homo sapiens

<400> 9

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<210> 10

<211> 2660

<212> DNA

<213> Homo sapiens

<400> 10

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<210> 11
 <211> 1647
 <212> DNA
 <213> Homo sapiens

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<210> 12
 <211> 1467
 <212> DNA
 <213> Homo sapiens

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<400> 12
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<210> 13

<211> 815

<212> DNA

<213> Homo sapiens

<400> 13

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<210> 14

<211> 779

<212> DNA

<213> Homo sapiens

<400> 14

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<210> 15

<211> 1230

<212> DNA

<213> Homo sapiens

<400> 15


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<210> 16

<211> 1135

<212> DNA

<213> Homo sapiens

<400> 16

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<210> 17

<211> 2950

<212> DNA

<213> Homo sapiens

<400> 17

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<213> Homo sapiens

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 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 783

<212> DNA

<213> Homo sapiens

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<210> 24

<211> 1724

<212> DNA

<213> Homo sapiens

<400> 24

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<210> 25
 <211> 1070
 <212> DNA
 <213> Homo sapiens

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<400> 25
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<210> 26
 <211> 2496
 <212> DNA
 <213> Homo sapiens

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<400> 26
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<210> 27

<211> 986

<212> DNA

<213> Homo sapiens

<400> 27

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<210> 28

<211> 212

<212> DNA

<213> Homo sapiens

<400> 28

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<210> 29

<211> 11

<212> DNA

<213> Homo sapiens

<400> 29

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<210> 30

<211> 386

<212> DNA

<213> Homo sapiens

<400> 30

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<210> 31

<211> 3104

<212> DNA

<213> Homo sapiens

<400> 31

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<210> 32

<211> 3104

<212> DNA

<213> Homo sapiens

<400> 32

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gccacggcca cactcaagag gagctctggc acctgcctgt ttgtggcgtg gaaacggctg 3060
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<210> 33
<211> 72
<212> DNA
<213> Homo sapiens

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<400> 33
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atggcctaca gg 72

```

```

<210> 34
<211> 1038
<212> DNA
<213> Homo sapiens

```

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<400> 34
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gggagtggtg gtgacggggt aggcataagg ggtgagagt ctgataagaa ggatgaggag 180
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cagagagaca gagtggatga agaggccttg aatttccctt acgaggatga ctttgacaac 360
gatgtggatg ctctgtctga agaaggcctt tgtgccccca aaaagaggcg aacagaggaa 420
aaatatggcg gagacagcga ccattccgtcc gatggagaga caagtgtgca gccgatgatg 480
accaagattt aaacagtgct caaaagtcgt gcccgccac ctacagagcc gctgcccgcac 540
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aaagtcgagg tgtgcaaaga tgaatccgtt gatctcgagg aatttcgaag ctacctggag 960
aagcgttttg actttgagca agttactgtg aaaaaattca ggacttgggc tgagcggcg 1020
caattcaatc gggaaatg 1038

```

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<210> 35
<211> 687
<212> DNA
<213> Homo sapiens

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<400> 35
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cacacctcga ctttggcctt cactgcccc agggcccccag ggctgctctc agccctagt 180
gggtctttct cgtccggggg ccccgggtca gcacccatag agtcaggctc atccagggga 240
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gaccagggtg ccacccgaga ctctctgtgt aggtacacc ggactccaga gttatggaat 480
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gttttaatct tggatcatat cggctgcaca cttgtctctc catcggaagg atggtcgtg 600
tctccgccat atttttctc tgttcgcctc tttttgggg cacaaggcc ttcttccagc 660
agagcatccc gattgaatc tagacct 687

```

```

<210> 36
<211> 960
<212> DNA

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<213> Homo sapiens

<400> 36

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atgcagcttg cccctttctat gtgggtgcgtg ttccaggcctt gacagatttt atcaaaagga 180
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aattctcagg aaatacagtt tatatcttcc tcttatgctc ttccagtcac caactactta 480
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tggtatataa acaactttta agaaagatca ttatctcttt ctctacctaa atatgaggag 780
tcttagcata atgacaaaata tttataatct ttcaattaat ggtacttgct ggatccacac 840
taacatctct gctaataatc tcattgtttc ttccaactga ttctaacac tatatcccac 900
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```

<210> 37

<211> 684

<212> DNA

<213> Homo sapiens

<400> 37

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cagagcacta aatattttta ggcaagtcca taggtctgaa tctcttaaga attctcgcc 60
tctgtgggat ttagggaagc attataaatg cattaatcct tatagtcaat tctgtgccta 120
ggattttgcc agggaacagt tcactgacta ggaaaagcac tacattttta attcagcatt 180
agtgcattgg gaaggatctt tactgctttg tgcttgcat gtcattattt tccatttgac 240
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tcactaaaac tctagaaggt gttacaaggg ggagggaagg ggggcaagt ccttgaacat 360
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cattgtagga aagcaattct gtacatgagt ttaagcattc ttgttgcat gtctctgcag 600
attctatttt tgtttacaat atcaaatgt atgttagcaa aatgggtgga ttttcaata 660
aaatgcagct tccacaaaag tttt 684

```

<210> 38

<211> 1510

<212> DNA

<213> Homo sapiens

<400> 38

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cgccgctttt tttttttttt tttttttttt tttttttttt tttttttttt aattttngga 60
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attattgcaa gtgttctaaa aaatcagaac aaaactaatt tattatagtt ctgtcttcat 180
tatacaccac gtgttggtga gttaaacaca acaaaattgt cttttctttt aaaagtgtct 240
actaaagata aaaagaataa gataacaatt aacatgtagt ttgttacatt aaaaaatctg 300
atatacatat ttctattgcc tgttagcttg ttctaagcct ctttaactat tacaacaaaa 360
aaaaaaaaag gaaagaaaaa gaaaattcat tgtttaaagg caaacattca attcagttga 420
tacaacatta cagtacagtc aactaacatc attcaacgaa ggtaacaagt ctagccttag 480
cttcttgagt taaaagtcta tagaccagat tgctacaaaa gtttcaatgc tgcctcaaaa 540
ccgtatgtta gcttttttga ggacaaagta ctttctacgg atggcttcag aaggggtcat 600
gctactggta aaagcacagg ggaaccccat cctgtcatta atcattttat tgagcactgt 660
agttagaaca gcattattga gtttagcaca acaactaaaa taaaataata atataataac 720
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gccgtgtcaa acccttgcca tacgctatac taaaaaaatt tgaatatcc acccgtctc 840
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ccccattact gcagcaagggt ctgtactggt ttcttgatca gagatgtcca ctgcgaaggc 1260
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atcgactggg accctggcag tatatgttat gtgagggtta tcaatcttca tgggtggcaga 1440
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ttctagacct                                     1510

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<210> 39

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 39

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tttaatatag ttatatattt aagcttaaaa ataatttagc ttctagagta ttacgttttt 180
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tcattctgta ttcttatca gatagtaagt aaactgtaag ttggagat tactgttttc 1260
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```

<210> 40

<211> 1659

<212> DNA

<213> Homo sapiens

<400> 40

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ggagccgagc tttagaccca ctgctaagga gttattgaag cacaagttta tactacgcaa 180
tgcaaaagaa acttctact tgaccgagct catcgacagg tacaagagat ggaaggccga 240
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ggggggcagt gattctggg acttgatctt cacaatccga gaaaaagatc ccaagaatct 360
cgagaatgga gctcttcagc catcggactt ggacagaaat aagatgaaag acatcccaa 420
gaggcctttc tctcagtgtt tatctacaat tttttctct ctgtttgcag agttgaaggaa 480
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ctggccaagt gcttctgtag ataacgtcag tggagtaaat attcgacagg ccataacttg 1200
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aatacgattt tctgttgca cttgtagtgg attctgcata tcatctttcc cactaaaaa 1620
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```

<210> 41

<211> 334

<212> DNA

<213> Homo sapiens

<400> 41

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acgcctttct gttccttgct ctcaccttac tccccctcagg accctacccc accctctttg 180
aaaagacaaa gctctgccta catagaagac tttttttatt ttaaccaaag ttactgttgt 240
ttacagtggag tttggggaaa aaaaataaaa taaaatggc tttcccagtc cttgcatcaa 300
cgggatgcca catttcataa ctgtttttaa tgggt 334

```

<210> 42

<211> 2456

<212> DNA

<213> Homo sapiens

<400> 42

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aataccaagt gtcagcatgt tagtaataaa cagggtgtctc taccattagt caaagggtggg 180
agttaagcct ttcatctttg tagctttctc cagtacctaa ccatgattta cttcatggga 240
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ccattggaaa cactgagctg gaaaaataat ttgcagaagg tcagtatcaa atggataagc 480
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gcaaatccct ctaggtgttc agcaagggtg ttgactttct aggctgctcg cttaccagtt 2100
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<210> 43

<211> 698

<212> DNA

<213> Homo sapiens

<400> 43

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aaaggagtat caggagtgtg atgagctgca gaagaagtta aatattaaca tttccctgga 480
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tgaaattgag gcgatgatca agagagtctg attggccaaa gaacaggaat cccgggcaga 600
ttgtatcagt gagtttatag aatggcagta taatgacaat aacacttctc attgttttaa 660
caaaatgacc aatctgaaat tagaggatgc aaggagag 698

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<210> 44

<211> 1346

<212> DNA

<213> Homo sapiens

<400> 44

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actcagagtg gaaatcttgt ccacagctac cgaggcactg gcggcatctt cgagggtgtg 180
tggaacgccc gaggagacaa agtgggtgcc agcgcgtccg acggctctgt gtgtgttttg 240
gatctgcgga agtaaccaca aaatattatc gaaaaaagaa aagaattcta atgaccagcc 300
gtgaatgtgt aggggttcag ctctattctc caaaactgta ggaacttgac ttgcgttaga 360
gtgtactctg aaaccaactc gtctctggcc gcaggagtct atatgttttc gtaatcttca 420
tcaagaagtt tttaaaaggc aagcaaaaac agaagcaaat catatcaaac ggggatagaa 480
tggtttccac tgaggacatt cagcctggga aggaggaagt caccagctcg agcgtgtgg 540
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aggaggttca aagaccagtt tgtaccgatg aaacgcgcaa ctttgtaate ccaacacttt 780
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<210> 45

<211> 1908

<212> DNA

<213> Homo sapiens

<400> 45

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<210> 46

<211> 1725

<212> DNA

<213> Homo sapiens

<400> 46

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<210> 47

<211> 1444

<212> DNA

<213> Homo sapiens

<400> 47

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<210> 48

<211> 929

<212> DNA

<213> Homo sapiens

<400> 48

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<210> 49

<211> 1676

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 565

<212> DNA

<213> Homo sapiens

<400> 50

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gaaatttctc agcagttagt gcatt 565

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<210> 51

<211> 2414

<212> DNA

<213> Homo sapiens

<400> 51

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<210> 52

<211> 1241

<212> DNA

<213> Homo sapiens

<400> 52

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 <211> 1109
 <212> DNA
 <213> Homo sapiens

<400> 53
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 <213> Homo sapiens

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<400> 55

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<210> 56

<211> 1919

<212> DNA

<213> Homo sapiens

<400> 56

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<210> 57

<211> 1919

<212> DNA

<213> Homo sapiens

<400> 57

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<211> 2837

<212> DNA

<213> Homo sapiens

<400> 58

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<211> 2482

<212> DNA

<213> Homo sapiens

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 <211> 1815
 <212> DNA
 <213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
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<213> Homo sapiens

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<211> 5209

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 67

<211> 261

<212> DNA

<213> Homo sapiens

<400> 67

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<210> 68

<211> 942

<212> DNA

<213> Homo sapiens

<400> 68

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<211> 1027

<212> DNA

<213> Homo sapiens

<400> 69

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<210> 70

<211> 668

<212> DNA

<213> Homo sapiens

<400> 70

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<211> 957

<212> DNA

<213> Homo sapiens

<400> 71

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 <212> DNA
 <213> Homo sapiens

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<210> 73
 <211> 2211
 <212> DNA
 <213> Homo sapiens

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<210> 74

<211> 4087

<212> DNA

<213> Homo sapiens

<400> 74

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<213> Homo sapiens

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<211> 2353

<212> DNA

<213> Homo sapiens

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<211> 1212

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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<210> 83

<211> 1327

<212> DNA

<213> Homo sapiens

<400> 83

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<210> 84

<211> 1922

<212> DNA

<213> Homo sapiens

<400> 84

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<210> 85

<211> 1432

<212> DNA

<213> Homo sapiens

<400> 85

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<210> 86

<211> 1662

<212> DNA

<213> Homo sapiens

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<400> 86
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tccgtctctg gaggtccccc atcagctgtc agccagccag cagcaaagca aattaagact 1620
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<210> 87
<211> 1662
<212> DNA
<213> Homo sapiens

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<400> 87
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<210> 88
 <211> 568
 <212> DNA
 <213> Homo sapiens

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<210> 89
 <211> 1091
 <212> DNA
 <213> Homo sapiens

<400> 89
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<210> 90
 <211> 1644
 <212> DNA
 <213> Homo sapiens

<400> 90
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<210> 91

<211> 1926

<212> DNA

<213> Homo sapiens

<400> 91

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<211> 598

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 93

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<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<210> 101
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<212> DNA

<213> Homo sapiens

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<211> 2391

<212> DNA

<213> Homo sapiens

<400> 103

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<210> 104

<211> 4116

<212> DNA

<213> Homo sapiens

<400> 104

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<211> 1651

<212> DNA

<213> Homo sapiens

<400> 105

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2863

<212> DNA

<213> Homo sapiens

<400> 108

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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 <212> DNA

<213> Homo sapiens

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<210> 115

<211> 1266

<212> DNA

<213> Homo sapiens

<400> 116

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<210> 117

<211> 716

<212> DNA

<213> Homo sapiens

<400> 117

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<210> 118

<211> 4598

<212> DNA

<213> Homo sapiens

<400> 118

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<210> 119

<211> 637

<212> DNA

<213> Homo sapiens

<400> 119

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<210> 120
<211> 1642
<212> DNA
<213> Homo sapiens

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<400> 120
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agaataaaag aatataagaa at 1642

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```

<210> 121
<211> 1000
<212> DNA
<213> Homo sapiens

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<210> 122

<211> 1355

<212> DNA

<213> Homo sapiens

<400> 122

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```

<210> 123

<211> 363

<212> DNA

<213> Homo sapiens

<400> 123

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<210> 124

<211> 3429

<212> DNA

<213> Homo sapiens

<400> 124

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<211> 1129

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 126

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<211> 1867

<212> DNA

<213> Homo sapiens

<400> 127

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<210> 128

<211> 4802

<212> DNA

<213> Homo sapiens

<400> 128

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<212> DNA

<213> Homo sapiens

<400> 130

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<210> 131

<211> 2584

<212> DNA

<213> Homo sapiens

<400> 131

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<211> 2690

<212> DNA

<213> Homo sapiens

<400> 132

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<210> 133

<211> 2146

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 135

<211> 1815

<212> DNA

<213> Homo sapiens

<400> 135

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<210> 136

<211> 755

<212> DNA

<213> Homo sapiens

<400> 136

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<210> 137

<211> 3039

<212> DNA

<213> Homo sapiens

<400> 137

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<210> 138

<211> 575

<212> DNA

<213> Homo sapiens

<400> 138

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<210> 139

<211> 1794

<212> DNA

<213> Homo sapiens

<400> 139

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<210> 140

<211> 691

<212> DNA

<213> Homo sapiens

<400> 140

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<210> 141

<211> 1570

<212> DNA

<213> Homo sapiens

<400> 141

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<210> 142

<211> 2702

<212> DNA

<213> Homo sapiens

<400> 142

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cc

2702

<210> 143
 <211> 3504
 <212> DNA
 <213> Homo sapiens

<400> 143

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<211> 3504

<212> DNA

<213> Homo sapiens

<400> 144

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<210> 145

<211> 1877

<212> DNA

<213> Homo sapiens

<400> 145

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<210> 146

<211> 2447

<212> DNA

<213> Homo sapiens

<400> 146

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<211> 2436

<212> DNA

<213> Homo sapiens

<400> 147

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<211> 884

<212> DNA

<213> Homo sapiens

<400> 148

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<210> 149

<211> 2872

<212> DNA

<213> Homo sapiens

<400> 149

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<210> 150

<211> 1253

<212> DNA

<213> Homo sapiens

<400> 150

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<210> 151

<211> 1444

<212> DNA

<213> Homo sapiens

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<400> 151
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<210> 152
<211> 619
<212> DNA
<213> Homo sapiens

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<210> 153
<211> 1728
<212> DNA
<213> Homo sapiens

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<210> 154

<211> 1264

<212> DNA

<213> Homo sapiens

<400> 154

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<210> 155

<211> 2855

<212> DNA

<213> Homo sapiens

<400> 155

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<210> 156

<211> 3220

<212> DNA

<213> Homo sapiens

<400> 156

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<211> 391

<212> DNA

<213> Homo sapiens

<400> 157

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<213> Homo sapiens

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<211> 779

<212> DNA

<213> Homo sapiens

<400> 159

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<211> 2310

<212> DNA

<213> Homo sapiens

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<212> DNA

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<210> 166

<211> 1942

<212> DNA

<213> Homo sapiens

<400> 166

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<210> 167

<211> 1359

<212> DNA

<213> Homo sapiens

<400> 167

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<210> 168

<211> 2961

<212> DNA

<213> Homo sapiens

<400> 168

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<210> 169

<211> 2162

<212> DNA

<213> Homo sapiens

<400> 169

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<211> 1613

<212> DNA

<213> Homo sapiens

<400> 170

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<210> 171

<211> 4160

<212> DNA

<213> Homo sapiens

<400> 171

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<210> 172

<211> 1185

<212> DNA

<213> Homo sapiens

<400> 172

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gagctacagc ctccaccagg agggcctgga accctcagcc tgcacttctt caaccctcag 180
gaagctcagc ggtgggcagt cctagtccga ggtgccaccg ttggaaggaca gaatggcagc 240
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<210> 173

<211> 1293

<212> DNA

<213> Homo sapiens

<400> 173

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tgacactcac cctgaccgga ctgggggttt aaggggtgtg gcaggaggtt ttggactcga 180
tgagtttcca ccgaaatgtc ggagaagtca ggcagagca caaaagcaaa ggatgggaaa 240
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gtaaacattg tacctaagaa tggcacaggg tgggcacaa aacaagagcg acatgaagaa 480
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1293

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<210> 174
 <211> 956
 <212> DNA
 <213> Homo sapiens

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<400> 174
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<210> 175
 <211> 348
 <212> DNA
 <213> Homo sapiens

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<400> 175
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ttgcctggaa tgtgtcccca tctctactct aagaaatgcg caatggactc tttggagaaa 180
gaagatattt taaaacattt ttagtgtgtc tgtaaatggt tcagcgtgta tcagatgttg 240
tcataggact cacatttctc tcagttatat ttaaaaccgt tgtgtacttt gtacaaagga 300
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<210> 176
 <211> 1019
 <212> DNA
 <213> Homo sapiens

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<400> 176
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aaattctttt tttttttttg agatggaatt tcccctgtca tcggggctaa agtgcagtga 180
gccgagatca caccactgca ctccagcttg ggcgacagag tgagactctg tctcaaaaag 240
gaaatatcag agttgagaat agaaggatgt agcatggaaa gtggaacaga tgatgttttt 300
gttgtcacia ataaggggag ctaaaacctg gectgagccc ttgtgagagg gagtacagag 360
ctgaattgtg lggataactt acatttttagg cagaggggtg agaaatcccc atttagctac 420
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<210> 177

<211> 1651

<212> DNA

<213> Homo sapiens

<400> 177

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<210> 178

<211> 2701

<212> DNA

<213> Homo sapiens

<400> 178

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agatacacgt acagtaacaa tacaaaaatg tgactgggtca aacagctcaa gttcacattt 180
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ataagtaaca gttttattaat tttttttttt acagtgagat atggctatgg gaagcagggtg 660
atactatttg ttttaagaac tgggatgcc aactaacact ggagttcccc aagactttgc 720

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<210> 179

<211> 1916

<212> DNA

<213> Mus musculus

<400> 179

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<210> 180

<211> 3720

<212> DNA

<213> Homo sapiens

<400> 180

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<210> 181

<211> 680

<212> DNA

<213> Mus musculus

<400> 181

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<210> 182

<211> 1849

<212> DNA

<213> Mus musculus

<400> 182

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```

<210> 183

<211> 466

<212> DNA

<213> Homo sapiens

<400> 183

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gagccaccag taactctcac atactcagca aactcaccgg tgggtcgcta ggggtgggta 360
tggggccatc cgagctgagg ccatctgggt ggtggtgggt gatggtactg gagtaactga 420
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<210> 184

<211> 744

<212> DNA

<213> Homo sapiens

<400> 184

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<210> 185

<211> 1203

<212> DNA

<213> Homo sapiens

<400> 185

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```

<210> 186

<211> 883

<212> DNA

<213> Homo sapiens

<400> 186

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<210> 187

<211> 1009

<212> DNA

<213> Homo sapiens

<400> 187

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<210> 188

<211> 1874

<212> DNA

<213> Homo sapiens

<400> 188

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<210> 189

<211> 1114

<212> DNA

<213> Homo sapiens

<400> 189

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<210> 190

<211> 1756

<212> DNA

<213> Homo sapiens

<400> 190

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<210> 191

<211> 2071

<212> DNA

<213> Homo sapiens

<400> 191

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<210> 192

<211> 310

<212> DNA

<213> Homo sapiens

<400> 192

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<210> 193

<211> 971

<212> DNA

<213> Homo sapiens

<400> 193

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<210> 194

<211> 1699

<212> DNA

<213> Homo sapiens

<400> 194

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<210> 195

<211> 2902

<212> DNA

<213> Homo sapiens

<400> 195

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<210> 196

<211> 3134

<212> DNA

<213> Homo sapiens

<400> 196

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<210> 197

<211> 3323

<212> DNA

<213> Homo sapiens

<400> 197

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<210> 198

<211> 1225

<212> DNA

<213> Homo sapiens

<400> 198

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<210> 199

<211> 2671

<212> DNA

<213> Homo sapiens

<400> 199

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<210> 200

<211> 1942

<212> DNA

<213> Homo sapiens

<400> 200

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<210> 201

<211> 628

<212> DNA

<213> Homo sapiens

<400> 201

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<210> 202

<211> 1877

<212> DNA

<213> Homo sapiens

<400> 202

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<210> 203

<211> 2340

<212> DNA

<213> Homo sapiens

<400> 203

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<210> 204

<211> 3428

<212> DNA

<213> Homo sapiens

<400> 204

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<211> 1887

<212> DNA

<213> Homo sapiens

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<211> 786

<212> DNA

<213> Homo sapiens

<400> 207

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<211> 1439

<212> DNA

<213> Homo sapiens

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<211> 2888

<212> DNA

<213> Homo sapiens

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<211> 1511

<212> DNA

<213> Homo sapiens

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<211> 2039

<212> DNA

<213> Homo sapiens

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<210> 212

<211> 1175

<212> DNA

<213> Homo sapiens

<400> 212

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<210> 213
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 <212> DNA
 <213> Homo sapiens

<400> 213
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<210> 214
 <211> 593

<212> DNA

<213> Homo sapiens

<400> 214

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<210> 215

<211> 1847

<212> DNA

<213> Homo sapiens

<400> 215

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<210> 216

<211> 1070

<212> DNA

<213> Homo sapiens

<400> 216

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<210> 217

<211> 1897

<212> DNA

<213> Homo sapiens

<400> 217

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<210> 218

<211> 2099

<212> DNA

<213> Homo sapiens

<400> 218

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<210> 219

<211> 2666

<212> DNA

<213> Homo sapiens

<400> 219

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<210> 220

<211> 2028

<212> DNA

<213> Homo sapiens

<400> 220

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 <211> 685
 <212> DNA
 <213> Homo sapiens

<400> 221
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<210> 222
 <211> 1109
 <212> DNA
 <213> Homo sapiens

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 <211> 1629
 <212> DNA
 <213> Homo sapiens

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<210> 224

<211> 1074

<212> DNA

<213> Homo sapiens

<400> 224

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<211> 2139

<212> DNA

<213> Homo sapiens

<400> 225

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<210> 226
<211> 983
<212> DNA
<213> Homo sapiens

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<210> 227
<211> 2438
<212> DNA
<213> Homo sapiens

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<210> 228

<211> 1510

<212> DNA

<213> Homo sapiens

<400> 228

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<210> 229
 <211> 1186
 <212> DNA
 <213> Homo sapiens

<400> 229
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 <211> 1057
 <212> DNA
 <213> Homo sapiens

<400> 230
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<210> 231
 <211> 1900
 <212> DNA
 <213> Homo sapiens

<400> 231
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 ccggcagcta ccagagattc actgactgct ataagtgtct ctaccagttg cagcctgcga 240
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<210> 232

<211> 943

<212> DNA

<213> Homo sapiens

<400> 232

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<210> 233

<211> 1974

<212> DNA

<213> Homo sapiens

<400> 233

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<210> 234

<211> 731

<212> DNA

<213> Homo sapiens

<400> 234

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<210> 235

<211> 919

<212> DNA

<213> Homo sapiens

<400> 235

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919

<210> 236

<211> 1348

<212> DNA

<213> Homo sapiens

<400> 236

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1348

<210> 237

<211> 2311

<212> DNA

<213> Homo sapiens

<400> 237

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<210> 243

<211> 2405

<212> DNA

<213> Homo sapiens

<400> 243

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<210> 244

<211> 1747

<212> DNA

<213> Homo sapiens

<400> 244

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<210> 245

<211> 1198

<212> DNA

<213> Homo sapiens

<400> 245

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<210> 246

<211> 1146

<212> DNA

<213> Homo sapiens

<400> 246

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<210> 247

<211> 2260

<212> DNA

<213> Homo sapiens

<400> 247

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<210> 248

<211> 1569

<212> DNA

<213> Homo sapiens

<400> 248

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<210> 249
<211> 2916
<212> DNA
<213> Homo sapiens

<400> 249
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<212> DNA

<213> Homo sapiens

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<211> 2547

<212> DNA

<213> Homo sapiens

<400> 253

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<212> DNA

<213> Homo sapiens

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<210> 261

<211> 2500

<212> DNA

<213> Homo sapiens

<400> 261

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<210> 262

<211> 815

<212> DNA

<213> Homo sapiens

<400> 262

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<210> 263

<211> 1946

<212> DNA

<213> Homo sapiens

<400> 263

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<210> 264

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 264

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<210> 265

<211> 3004

<212> DNA

<213> Homo sapiens

<400> 265

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<210> 266

<211> 1863

<212> DNA

<213> Homo sapiens

<400> 266

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<210> 267

<211> 2341

<212> DNA

<213> Homo sapiens

<400> 267

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<210> 268

<211> 507

<212> DNA

<213> Homo sapiens

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<211> 2854

<212> DNA

<213> Homo sapiens

<400> 270

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<211> 2528

<212> DNA

<213> Homo sapiens

<400> 271

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<211> 3427

<212> DNA

<213> Homo sapiens

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<211> 3355

<212> DNA

<213> Homo sapiens

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<211> 1339

<212> DNA

<213> Homo sapiens

<400> 274

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<210> 275

<211> 638

<212> DNA

<213> Homo sapiens

<400> 275

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<211> 2584

<212> DNA

<213> Homo sapiens

<400> 276

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<211> 891

<212> DNA

<213> Homo sapiens

<400> 277

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<213> Homo sapiens

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<211> 3705

<212> DNA

<213> Homo sapiens

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3705

<210> 280

<211> 1265

<212> DNA

<213> Homo sapiens

<400> 280

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<211> 2666

<212> DNA

<213> Homo sapiens

<400> 281

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<210> 282

<211> 981

<212> DNA

<213> Homo sapiens

<400> 282

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<210> 283

<211> 1811

<212> DNA

<213> Homo sapiens

<400> 283

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<210> 284

<211> 1472

<212> DNA

<213> Homo sapiens

<400> 284

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<210> 285

<211> 564

<212> DNA

<213> Homo sapiens

<400> 285

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<210> 286
 <211> 695
 <212> DNA
 <213> Homo sapiens

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<400> 286
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<210> 287
 <211> 694
 <212> DNA
 <213> Homo sapiens

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<400> 287
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<210> 288
 <211> 1393
 <212> DNA
 <213> Homo sapiens

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<400> 288
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<210> 289

<211> 1733

<212> DNA

<213> Homo sapiens

<400> 289

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cttgctgaat taaatattta tgagtgtgac atttttaagt atagtgaaca agacaccata 180
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<210> 290

<211> 2195

<212> DNA

<213> Homo sapiens

<400> 290

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<210> 291
 <211> 305
 <212> DNA
 <213> Homo sapiens

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<400> 291
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<210> 292
 <211> 819
 <212> DNA
 <213> Homo sapiens

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<400> 292
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<210> 293
 <211> 1057

<212> DNA

<213> Homo sapiens

<400> 293

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<210> 294

<211> 1794

<212> DNA

<213> Homo sapiens

<400> 294

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<210> 295

<211> 447

<212> DNA

<213> Homo sapiens

<400> 295

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<210> 296

<211> 3858

<212> DNA

<213> Homo sapiens

<400> 296

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<210> 297

<211> 2512

<212> DNA

<213> Homo sapiens

<400> 297

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<210> 298

<211> 1107

<212> DNA

<213> Homo sapiens

<400> 298

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<210> 299

<211> 1051

<212> DNA

<213> Homo sapiens

<400> 299

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<210> 300

<211> 1669

<212> DNA

<213> Homo sapiens

<400> 300

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<210> 301

<211> 2154

<212> DNA

<213> Homo sapiens

<400> 301

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<210> 302

<211> 5770

<212> DNA

<213> Homo sapiens

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<210> 303

<211> 798

<212> DNA

<213> Homo sapiens

<400> 303

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<211> 1279

<212> DNA

<213> Homo sapiens

<400> 304

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1279

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<210> 305

<211> 1398

<212> DNA

<213> Homo sapiens

<400> 305

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<210> 306

<211> 896

<212> DNA

<213> Homo sapiens

<400> 306

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tagttttgta aaaataaaac cagatttttct ccaaattttc tctaataattt tactctcaaa 180
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accattaat tacttctatt ttgaatgtac gtctacaatt atcctgtggg agaaaaagta 420
gttttagtat cttcacaaac ctacagtttt taaaataaat tagtttaaat aaatttctat 480
aattctcagg atgatctcac atttaatgaa cagactatgt tcaatatgga aactcaagaa 540
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<210> 307

<211> 2232

<212> DNA

<213> Homo sapiens

<400> 307

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cgcaggcggg cg 2232

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<210> 308

<211> 654

<212> DNA

<213> Homo sapiens

<400> 308

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aagactttaa cagcatctga aatgctacct ttattggatc attggaatac tcaactaaa 180
aagggtatcac tcagagaaat aatgtcagaa gaaattgcct tacaggaaaa acataatttg 240
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aagtcataag agaaaaagcc aaagaaatta aaagagactg aagaaacacc aagtgaactg 540
tctttccagg actttgagta cccagactat gatgactaca gagcagaggg tttcctttac 600
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<210> 309

<211> 610

<212> DNA

<213> Homo sapiens

<400> 309

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tcctttttag tatagtggta cttaaaatca ctggttcact taaaaaaaca aacaataaaa 180
tgttaaaactc tactaatgta caaataagct gaaaagtgc attttatgtg tattttttgc 240
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tttatttttg aaagatatga ttgtattatg tgcaactcag ttgcttacat tataactaca 540
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gctgctaagc 610

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<210> 310

<211> 1064

<212> DNA

<213> Homo sapiens

<400> 310

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tcggagaaga ggtagaaaat gtggcagagg ccataaagga gaaaggcaaa gaggaacccg 180
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atcttacctg atatcactaa agatgaactc ttcaaaatgc tctgtactag gaaggatcca 780
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tttccttatg tataattttc cagatgggtga tgttactttt cagtgtactc atatgtctca 1020
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<210> 311

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 311

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<210> 312

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 312

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<210> 313
<211> 994
<212> DNA
<213> Homo sapiens

<400> 313
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<210> 314
<211> 795
<212> DNA
<213> Homo sapiens

<400> 314
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<210> 315
<211> 1526
<212> DNA
<213> Homo sapiens

<400> 315
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<210> 316

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 316

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<211> 1316

<212> DNA

<213> Homo sapiens

<400> 317

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<211> 787

<212> DNA

<213> Homo sapiens

<400> 318

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<210> 319

<211> 2804

<212> DNA

<213> Homo sapiens

<400> 319

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<210> 320

<211> 1604

<212> DNA

<213> Homo sapiens

<400> 320

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<210> 321

<211> 2425

<212> DNA

<213> Homo sapiens

<400> 321

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<211> 1558

<212> DNA

<213> Homo sapiens

<400> 322

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<210> 323

<211> 975

<212> DNA

<213> Homo sapiens

<400> 323

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<211> 1782

<212> DNA

<213> Homo sapiens

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<210> 325
 <211> 830
 <212> DNA
 <213> Homo sapiens

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<400> 325
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<210> 326
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 <212> DNA
 <213> Homo sapiens

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<400> 326
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<210> 327

<211> 2067

<212> DNA

<213> Homo sapiens

<400> 327

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<210> 328

<211> 1998

<212> DNA

<213> Homo sapiens

<400> 328

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<210> 329

<211> 1355

<212> DNA

<213> Homo sapiens

<400> 329

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<210> 330

<211> 1388

<212> DNA

<213> Homo sapiens

<400> 330

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<210> 331

<211> 2633

<212> DNA

<213> Homo sapiens

<400> 331

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<210> 332

<211> 2029

<212> DNA

<213> Homo sapiens

<400> 332

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<210> 333

<211> 1754

<212> DNA

<213> Homo sapiens

<400> 333

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<210> 334

<211> 1613

<212> DNA

<213> Homo sapiens

<400> 334

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<210> 335

<211> 1733

<212> DNA

<213> Homo sapiens

<400> 335

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<210> 336

<211> 1684

<212> DNA

<213> Homo sapiens

<400> 336

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<210> 337

<211> 1288

<212> DNA

<213> Homo sapiens

<400> 337

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<210> 338

<211> 679

<212> DNA

<213> Homo sapiens

<400> 338

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<210> 339

<211> 1531

<212> DNA

<213> Homo sapiens

<400> 339

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<210> 340

<211> 1478

<212> DNA

<213> Homo sapiens

<400> 340

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<210> 341

<211> 524

<212> DNA

<213> Homo sapiens

<400> 341

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<210> 342

<211> 1823

<212> DNA

<213> Homo sapiens

<400> 342

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```

<210> 343

<211> 1381

<212> DNA

<213> Xenopus sp.

<400> 343

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tctttggcaa actggcgagt ggcagatctc tgcctcaaac ttatgtggtt cgagaagacc 480
tagttgctgt ggaggaaatt cgtgatgtta gtaaccttg catctttatt taccacttt 540

```

```

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agatctgtca agagtgaagag gcaacagata gagtgtcctt ggtaataaga agtcagagat 720
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c 1381

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<210> 344

<211> 1554

<212> DNA

<213> *Xenopus* sp.

<400> 344

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cagttcttcc gtctccttca caagtccctc tatttcaact tgaccaaggt ggcagaggac 600
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaact cgag 1554

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<210> 345

<211> 1998

<212> DNA

<213> *Xenopus* sp.

<400> 345

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gtgcttcttg gcgtgtggct cgcattctat gtatctggac ttctttggca gctcctcaag 180
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<210> 346

<211> 1145

<212> DNA

<213> *Xenopus* sp.

<400> 346

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tgttttgtct tgcctcttgg cgtgtggtc gcaatctatg tatctggact tctttggcag 180
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<210> 347

<211> 1140

<212> DNA

<213> *Xenopus* sp.

<400> 347

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```

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```

<210> 348

<211> 807

<212> DNA

<213> Homo sapiens

<400> 348

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ccattaaaaa aagatttctt ttctgcc 607

```

<210> 349

<211> 533

<212> DNA

<213> Homo sapiens

<400> 349

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taacattaga aaagtgtat ttgccctcaa ccaaatggaa agaaagagag ggaaaaactat 180
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<210> 350

<211> 1127

<212> DNA

<213> Homo sapiens

<400> 350

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caaaaaaatt agctgggtgt ggcagtgtgc gcctgtagtc ccagctactt ggggggctga 60
ggctggagta ttgcttgagc ctgagaggtc aaagctgcag tgagccataa ctgagctact 120

```

```

gcactccagt ctgggcaaca gagcaagacc ctgtctcaaa caaaaccgaa accaaaaaca 180
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<210> 351

<211> 812

<212> DNA

<213> Homo sapiens

<400> 351

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<210> 352

<211> 669

<212> DNA

<213> Homo sapiens

<400> 352

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tggaatggaa catgagggtat atatctttgc ctttataatt ttaacatctt atattgaaga 540
ttctgaaaac ctatctttat tagaggaaaa tctcaatctt cagttttggc cttctgtcag 600
cagaatgata agtgcaatag ttgtaaatct acttgacact gtaataaact gaactgaact 660
ttcaaagtc 669

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<210> 353

<211> 888

<212> DNA

<213> Homo sapiens

<400> 353

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gctctgcaga aaacccttcc ctggaactcc cagatcattg acaggcctga gagttttcca 180
tacggcctgc accctaacct ctgggaagaa aatatccaca atgaaatttc tacaagatta 240
gaggaaggag agaggcaacg gggattccat ttctactagg agtatcaacc tctgagaggg 300
atatatccat ctctgtggat gtcatctgct ctgcagaaaa ccccttcttg gaactaccag 360
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ttccagccct gcccttctca acacgacata tagacaaccc caggctcgtg gtccctagag 480
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```

<210> 354

<211> 1561

<212> DNA

<213> Homo sapiens

<400> 354

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cccctcccgg ctcccttcca ctctgcaga ggcgcacaca cgcgcgctgg ctccctgccc 180
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tggggagctt ctgttctggt gaagggaccc gggcaggccc ccagcacccc atgctgactt 600
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gcgtttgctt tagcggatat gtttatacac atgaataaa aatgtttttt ttctttgggc 1440
tttttgcttc tttttcccc ccttctcac ctctccctct ccccgacccc acccccaaaa 1500
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t 1561
```

<210> 355

<211> 1997

<212> DNA

<213> Homo sapiens

<400> 355

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atatcattac catatgatct aatgtgggtg tcagccggat tgtgttcatt gagggaaacc 180
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cacctacccc ctctcctttt ccacacctgc aaactctttt acttgggctg aatatttagt 300
gtaattacat ctacagcttg agggctcctg ttgcaaattc ccgattaaa aggttccctg 360
```

```

gttgtgaaaa tacatgagat aaatcatgaa ggccactatc atcctccttc tgcttgacac 420
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aggcttctgg gataggccca gaagtctctg atgaccgoga cttagagccc tccctaggcc 540
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tggacaaagt gccaaaggat cttccccctg acacaactct gctagacctg caaaacaaca 660
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ctgttgatgt taactgagct actagagata ttcttatttc actaaatgta aaatttggag 1740
taaatatata tgtcaatatt tagtaaaagt tttctttttt aatttccagg aaaaaataaa 1800
aagagtatga gtctctctga attcattgag cagttagctc atttgagata aagtcaaatg 1860
ccaaacacta gctctgtatt aatcccatc attactggta aagcctcatt tgaatgtgtg 1920
aattcaaac aggctatgta aaatttttac taatgtcatt attttgaata aataaattta 1980
aaaatacatt caaaatt 1997

```

<210> 356

<211> 909

<212> DNA

<213> Homo sapiens

<400> 356

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aaaatatata ttaaaatggt ctctaaatat ttctgtcttc ttgcaggtct ctttttacta 60
gatcatggct gttcttccca cctcatccct ctgaaaataa aaatgtattg ccttccccac 120
catccatcat agccaggcca ctaacttgac ttggtgcaag agattcttgc tgcgaacttt 180
gtagagccag tgtgcagata gaatttggct ttgagggttc ctgatggctt tttagtcttt 240
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ttacttcatg gtactagaag accttctctg ccactctctc cacatgagag agtcagctgc 360
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tgagggatag ttttctttga taagaaacct ggagtccatt tactctgacc tctctttaa 480
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gctgtccttt tgcctttacg cccacccca actccctta aattttacag gcttatgaca 600
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ttcaggcagt ctcttgggga agagtatgcc accatccgaa tatcaggcac tgagtgggat 780
gtgggtgatg ctacatgac tggctagagc tttggggggg ggggtggggg ttactactat 840
tttttgccca tgatttcttt ccccttctt ttttttttaa ttaataaat ggatcaaatt 900
aaataattc 909

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<210> 357

<211> 1123

<212> DNA

<213> Homo sapiens

<400> 357

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aagcatcgct tgggggtcag ttttctgtca aacaacttgg cggcttccca ggaccgaagg 120
tcacccccca accagaatac aatccgcggg aactgttcca ggctcccgcg cctccaagct 180
gtagctatga cggcgcgcg gactccgagc cgttctcttg ccagcgttct ccacaacgga 240
ctgggtcgct atgtgcagca gctgcagcgt ctgagcttca gcgtcagccg cgacggcgcc 300

```

```

tcgtctcgcg gcgcagggga gttcgtggag cgggaggtga tcgacttcgc ccgacggaat 360
ccaggggtcg taatatatgt aaactcgcgt ccgtgctgcg tgcccagagt agtggccgaa 420
taccttcaacg gggctgtgcg cgaggagagc atccactgca agtcgggtcg ggagatctcg 480
acgctggtgc agaagctggc cgaccagtcg ggcttgagc tgatccgcac ccgcaagccc 540
ttccacaccg acaaccctag catccagggc cagtggcacc ccttcaccaa caagccgacc 600
acgttcgcgc ggctacgccc ccgagaggtt caggatcctg cccagccca ggtgcaagca 660
cagtgaagag ttgccccacc aactgcagcc ccaggctttg gactgttact ccggtaaagg 720
tggtttcttc cctttgggat tccaagccca ggcaaatgga acccatcaat gggcaagtgt 780
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gaacaaccac tgagctacgg agagctctgc tgtgatgggc taggcacttt atatctgtgt 1080
gaatacagat ttataaaaaca ggttaataaa cttatccaag gtc 1123

```

<210> 358

<211> 382

<212> DNA

<213> Homo sapiens

<400> 358

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ggggatctct gagccaatcc aagccatgca gaggccaaag ggattaggac ttggatttcc 60
tctacaaaaa agtacttccg caactactac ccccaatgca ggaaaatccg cctaagaaaa 120
gcaaagaaga aatgttttac agactttatt cactatgtcc cattgttcta aaatgataac 180
atgacttctg tttttgaagc aaaaatctac attgcctcaa acacatcact ctacttccct 240
tactgcatac agtctgcca tagtgagaga aatgggattt catcacaatt catggtgcta 300
aaatgaaaac ctctgcactt taattttttt cagtaatttc cagctatttc taggtataaa 360
gagcagctcg tttctcttat tt 382

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<210> 359

<211> 1274

<212> DNA

<213> Homo sapiens

<400> 359

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ctgcgaatgc ggatcaagct tacatataat cacaagggct cagcaatgca agatctagca 60
gagggtgaaca actttccccc tcagtctgg caatgagggt ttggcaccat tctcattctt 120
tatccactcc aatcaaggga actctgggaa ggaggttgtg attgctggca agtccccccc 180
aactgtacca cgggcatgag gagctgaaga gaactgctga ggaggatttt cctaaggtaa 240
ctgctgacct tgaagcattg ttaaagacta atgtcctctc ctccactgtt gaggetggct 300
gcttctggag gctactttgc actcttctc ttctcctttt tccgcacttc tccacccctc 360
ccacatttac agccagaatc aacattccct gggcccctga ggaaataagc agctggtctg 420
gaggagagga ctgcaatcca tggcgaaaaa aactcactt tgtctctgca gcaaagagtt 480
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aatggacatt agggagccct gcctttttct actggttccc ccaatgtttg aaagaggcat 660
taggctcctg gttagccttt ctgtgcattg ctgtatacac acagaacaca cacatgtatg 720
tttggttacc aagaactggc cagaccttgc gagtttatlt gtaaacactg gacagatgga 780
gttaaaaaag agcttttgtt gagatttggc atgaaggata tgggtgctcta ttgtaatag 840
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cagactctgt atcaaaagta cctttgccct taggaagagt gagtattgga gtcattctat 1140
ctattactcc aaacctccct ttttatttct tgagcctggc ttggaccttg gcattccgtt 1200
tgaattcctt ctaactggaa catttgtgtt gtatctgtaa cactggcact gaaataaaga 1260
ccacacgggt aaag 1274

```

<210> 360

<211> 571

<212> DNA

<213> Homo sapiens

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<400> 360
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ccaggggcct ggtcatcggg cagctgagca gcpacttctc ggaggagggt ctgctccggg 180
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gctttggcgt ccccgcttc ggccacgtgc aggttgcct caataccct gtcctcctgg 480
tcctctggag gaaacctatg cccagagga aggacaaagt ccggtgacct ctgcccagac 540
acagactggc aataaactcc tactaaatcc c 571

```

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<210> 361
<211> 974
<212> DNA
<213> Homo sapiens

```

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<400> 361
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gaagtttctg aatgaaaaga cagatctctg gattcagact ccaggcagaa gctgcttaac 480
agcaaaaatc tggcatcttc actacatttt aagattttag gtggaactaa gagggatcag 540
atatagagga ataaggaatg tgagaaggaa aaagatatag tagtttagct aaatttttct 600
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gctaaaagag acacaaatag cttctctttt accttggtct taaggaaaag ccattttatt 720
aacaaaagta ttagacacga ctgcataaga aatttgctgt gtgagaataa agaacaagg 780
agtaggaggg tgggacagag aagggtgaga agttggcttc gtgagggcca cctgtcagtt 840
gtctttgtgc cttgtgacat caaaactgaa atggttgat tactgtgtc catgactttt 900
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ttcttacctc cccc 974

```

```

<210> 362
<211> 593
<212> DNA
<213> Homo sapiens

```

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<400> 362
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ctttttgcta ttgtgacaac attgtgtctg gtccgaaaat tcacctctgc agttcgagaa 120
gaacttttca aggccctagg gcttcataaa cttcacttac caaatacttc aagggtatca 180
gaaacagcca agccttctgt aaatgggcat cagaaagcac tgtgagacgc acagacggcg 240
tcttctgcca ccaagagacc cgagaactcc agattcacga cattcctgtc ccatgtagaa 300
gcatttccat tcaacogtgg cccctcttca gaacctagac ctatcagtgc catttttttt 360
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ccctgtagtt tccagttaag tgcagattcc ttacagacat atagaacagc gcatttttct 480
gtagacattt gctcatgttg gtaaatacaa tcacccatat gaaaaaattg ttttcacctg 540
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```

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<210> 363
<211> 900
<212> DNA
<213> Homo sapiens

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<400> 363
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agttataaat gttagccctg gacagatgtt aacaccagta aagtctagtt acagagtaaa 180
acctcagttt gtttaacttt atagaacaaa tggagaggaa gacagagaat catttaagag 240

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```

tggactagag agatcagatt ttgaaatagc tatatgcatg tgtttgtntg tgagacaggg 300
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tataaaactg gtaagtatta tagttgtcta ttttcctttt ttgactgaat ctaaaaaaca 780
cactttgcat gttttcacat ttataaatac ctttcttaga gcttcatact gtttcattgt 840
gcttatgagt tatgatattt aaatgtgaaa acatgcaaag tgtgtttttt agattcagtc 900

```

<210> 364

<211> 349

<212> DNA

<213> Homo sapiens

<400> 364

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cgaagtgttc cctctgggga gccaggtcgt gagaaaaat ctaactctcc aaaacatgtt 60
tattctatag catcaaaagg atcaaaattt aaggagctag ttacacatgg agacgcttca 120
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ggcttcacac cggaaatagg aaagaaaaaa cacacggaaa gtacccatt ctggtcgatc 240
aaaccaaaca atgtttccat tgttttgcac gcagaggaaac cttatatgga aaatgaagag 300
ccagatgacc ctctctttgc acaatagata aaagtcttta tatgaatat 349

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<210> 365

<211> 7

<212> DNA

<213> Homo sapiens

<400> 365

tagacca

7

<210> 366

<211> 631

<212> DNA

<213> Homo sapiens

<400> 366

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cgctctcggt gagagagcgg tctgagcgag tgcgtttgtg taaccgggca gagctaacac 60
ctgagctggt aaagatcctg cattctcagg ttgctggcag actgatcacc cgtgcagagg 120
agctggccca gatgtgaaa glggtgaatc tcccaacaga tctgtttaat agltgatga 180
atgtgggtcg cttcacggag gagatcgagt ggctgaagtt tttagccctt gcttgcagcg 240
ctctgggagt tactattacc aaaactctca agatagtgtg tgagggtctta tcatgtgacc 300
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ccaaagtgga tggggagatc tctgcatcac atgtcagcag gatgctaaac tacatggaac 420
aggaagtaat tggccctgat ggtataatca cagtgaatga ctttacccea aaccccgagg 480
ttcagctgga gtaaaagcac aattttggca attttaagg aagatacaga gatgattgta 540
cttcagaatg actgaaaccc atataccacc caaaatcaat tttctgtac aactgggtaca 600
cactaataaa caattaaaca tatgagatca g 631

```

<210> 367

<211> 1143

<212> DNA

<213> Homo sapiens

<400> 367

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tggcagccaa ggaggggctt ttgctgtgct aaattaggat ttgaggggtg gggaccctca 120
ccgaattcat tgattactga aaattgaatg ttttttgggt ccacatttca aggtgaagt 180
gtatagtgtg tatataacct ttcctatgga aatgtgacat tgagtacatt ttgtgtgtgt 240
gttgtgaagc cattaatata aatctttggg aatgaccac atctctatat gtatgtgttc 300
ccacttgtgg gagcaggcac taatgaaatc ctgtgcctgg aatggagata tttaggtacc 360

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tgaggcttag tgtcctgtgg tctgcatgta agatagatga catcctagaa caaagaagct 420
gttttaactt aatccccctg atcagcagga tctgctgtgt cagtgcacac atacattctg 480
tatctagaag tctaaaattt ctgcctttct cctaaagaat gtgttcttgc attttggttg 540
aaataacctt cacagtgtta aaaatcagat acctccttta gtgaccagtt caaattttaa 600
tagcgatagg tagccccctg gaaatttata actataactc cacaggaaat atgacttggg 660
agtgtctctg gtactaaaca aaataaagcc cctctttgca tttaaaacca aagtcacaaac 720
aaaactcttg taatgcaatt aattaacttt atgtcttccc atgactcaag ttttggttaa 780
tatgcccaaa aactttgatt ggcagtttct tcggttaatt attcctatag aatgtatatt 840
aagaaatcta tacaaattgg atatatgctt ggtaattctc cagtttctag gaggtaccta 900
tttctaccgt ttcaagtgat gaagtgaata taattttacat tcgatagtgt tactgataac 960
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aatgtataga taggtttgtg aaagtctaaa taatggttgt atagatatgt atatatggtt 1080
cacatatctg gatctgtgta tttgattttg tacttttaaat gtgacaaata aaccttttgg 1140
gag 1143

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<210> 368

<211> 748

<212> DNA

<213> Homo sapiens

<400> 368

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agttgtggtt taaaccagga gtgcgccggt tccgttcacc gcggcctcag atgaatgcgg 60
ctgttaagac ctgcaataat ccagaatggc tactctgac tatgttgata aggaaaatgg 120
agaaccagga acccgtgttg ttgctaagga tgggctgaag ctggggtctg gaccttcaat 180
caaagcctta gatgggagat ctcaagtttc aacaccacgt tttggcaaaa cgctcgatgc 240
cccaccagcc ttacctaaag ctactagaaa ggctttggga actgtcaaca gagctacaga 300
aaagtctggt aagaccaagg gacccctcaa caaaaacagc caagcttttc tgccaaaaag 360
atgactgaaa agactgttaa agcaaaaagc tctgttcctg cctcagatga tgccatacca 420
gaaatagaaa aatctttccc ttcatcctct agactttgag agttttgacc tgccgaaga 480
gcaccagatt gcgcacctcc ccttgagtgg agtgcctctc atgatcctg acgaggagag 540
agagcttgaa aagctgttta agctggggcc ccttcacct gtgaagatgc cctctacacc 600
atgggaatcc aatctgttgc agtctccttc aagcattctg tagaccctgg atgttgaatt 660
gccacctggt tgctgtgaca tagatattta aatttcttag tgcttcagag tttgtgtgta 720
tttgtattaa taaagcattc tttaacag 748

```

<210> 369

<211> 550

<212> DNA

<213> Homo sapiens

<400> 369

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tgagagaagac ctagaattta aagaacaaaa ggaacgtgaa gatgagtcct cctctatggt 60
tgacgaatat tttcaagaat gccaggatga atgaagaggt tactaaaagt aacctatcaa 120
agagcttggt gccaaaccag cagaacatto ttctcttcaa aggatgcaat agtagaaagc 180
tacttatttt aatgaaaaaa agtaaaactt cgctctttat cagcctcatg cctgaatcaa 240
atttttaatt attctgaaac tgctgctggt taaagtggaa tcttttagta ttataacagc 300
atcacttttag attttgtaag tcaaaattga aatgaatgca catagattta tatataaatt 360
agcacctgag ctaaggttaa ggctgggtcta aacttatttt cactttttgt attatttttg 420
agatgcagga attactgtta caaaatatgt atgtccgaag ggaaaaagct gcaaggatat 480
atataagacc accgcctatc tgtatcttcc caatttccca tattgaaaat gtatattatt 540
tatataactt 550

```

<210> 370

<211> 651

<212> DNA

<213> Homo sapiens

<400> 370

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aaatatacag tcttcccact tcactaacca aattcctact ttccagtgtt acttcccaat 60
ttatgcagga aacctcctgc aaagctgaaa ctgattagaa aattctttat attttaaaat 120
agctctttct catttttaga gaagtcaaat agccaacat caaaattaag aataaattga 180
attgtcacag tccattacag ttattgttgc tagatccacc tcatttgcag atgtcccaac 240
ttaaattcat ctgttcttaa aatgctactt aaaacttttg ttgttttctt gtaatatata 300

```

```

agaaaaagtt aatttatcaa ttgattgaat acagttttta ctaattagtt tatcaaacca 360
aatactgtga acgtaccagg tgtttacaga tttaaatgca tgttaccata gaaactatta 420
aagtaactag aactgtcaaa taacaaaacg gctcatgttt ttaaaatata tgtaactcat 480
tttaaaatat attaaattgt attccaaacc tgttctctctg tttctgtggc acctagggtt 540
aaaatagtga ttaatgtgta aatcacaaagt aaaatgaatt ctaatgtaca agtttgtttt 600
aaaaagtgta tgtcaagctt ttattttacac aataaaatgt tattaaagat g 651

```

<210> 371

<211> 635

<212> DNA

<213> Homo sapiens

<400> 371

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ggttatttta aatataaata gctaattgggg gtggtaggcc tataaaatta aatgccttgt 60
ataaaatcca aaatgaatgc aaaattgttt tcaactgtat tgactttatg ttgtatgatt 120
ccaatctctg ttctgttttg cacttgtatt taattcttca cctttgtaag acatttgtat 180
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gcatgttttc tttgtttcct ggcaatacga cgtgggaatt tcaatgcgtt ttgtttaga 360
tgctaacgtg tcagaatccc ttacattcaa cttttctaaa aaaagcattt ccagtcctgt 420
agtgtgtgct acagtaacca aattgttgaa aatggtttca agttattcaa atttgtacag 480
gactgtaaaag atattgtgac agcaaaatgt tgaaaaaaa agcctataga ataaaagcca 540
aaaagtatat attaggatct gcaaacaaatg aaaaattatg taatatattg tacaatatga 600
agcaagggcc ctgaataaaa atgccatagt ttgtg 635

```

<210> 372

<211> 1192

<212> DNA

<213> Homo sapiens

<400> 372

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cagtgtctga gtaaacatac gtgtgcgtgt gtctttatag tagcgtgatt tgtttaagaa 60
agtaacagag cagggattag agtccaagta atttggctcc agcactcctg cactacttaa 120
tacattttgt tggttggtta gtaataaaat actgtacaaa tggcaagata ggccagacgc 180
tggtgtttca ataaagcaaa ctcatcttaa ccatgaaagt gactcagctt gagatttaat 240
taatatgttt tctatgtgtg aggatctttc tttttatggc ctttggcagt aaaaatgatc 300
aagcgttttt atagaatgta taaaatgtgg ctttttttgt gtgttaataa ctttatgacc 360
ttgagtttac tgatcctgac gaagctcctc ttttctctct tttgcccact aaagatccat 420
tttatttatg cacacagtta aagccattgt agtgtagtgg aaacagcaca tattggattt 480
gtgtgttctt acattttaat tccagcatta tccattacta gctgtgtgac tggacaaatt 540
atacatcttt agaacttccc ttttctaacc tgtaaaatga gggaaattaa atcttcttca 600
ttggatagtt gtaaggagta aatgggatga tatatttttt aaatgcctgc tgtactactt 660
actgtatggc agatattcaa aaaattgtga gtgctttact tcttaataaa tgaaacacgt 720
ccaaatttaa gtactttttt ttcccttata gttgctaatt tttgtagggt aactctgtgc 780
ttgccaaaaca cttggtagcc agacctttag aatttgaacc agatactata gagttcctaa 840
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ggtgtctttt gccaaagagt atttctctgc tgtatcggag gaggaacaat ggaaaggaaa 960
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atcacatttt agttggacat gtaaaaagca agtagggaaa cttgggaaaa ttctcacaaa 1080
aggtagcttt ttttctaaaa aatttctctc tgatttttca gtaatgatgt agagagctgt 1140
agtttacaag ctgattttag aaccgtgtat taatgggaaa ggccaaagaa at 1192

```

<210> 373

<211> 1279

<212> DNA

<213> Homo sapiens

<400> 373

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ttccaatagt ataaaaacat tgttagcgac tggacaatta cctcattcaa caatgtttca 60
aataatgtat tatattaaaa ttagatgtct gataagttct aagaaatatt tatacctttt 120
tatatggaaag ataatttata tcatccatgt ttagtgcttt ttaaacatca actttacttt 180
ctaggtaatg tggctgtgca atattttttt aattttatct ttttactttt ctattacttt 240
ttcatatatt ttgtaccta agtatttcag tgaacttta agcccatacc tgtgtctgat 300

```

```

gtttattatt ggctttccac aattcttaca tcagactaca ttatattaga gaccattatt 360
gctagaatag catggtgattt aaaattttct aactctgggg gtattattta gtttaattatg 420
gattttttctt ttccacatttt actgtgtttt taactgggaa alaagattat ggctgtctaca 480
ataatttttt tgaatccac ttctgtgttt ctaaaataca actttatcat tgcaatccaa 540
ccaggtagtt catagaaaac tgtntttaat accagttttt ctataaagtc attactgttg 600
cttaaacata ttctatgcct attaaaatat attttctact ggtgatttca acattatttc 660
tcatactgac ttttattact ggaaatgttc ctgtacatgt tggcagcaga taaagatttt 720
tgaatgtttg aatgccctct gccttgattt ggttggaatt tttgctaaat tgggtaattg 780
gcttgaactt tatgactaca ttttctttta acttttttca tggacttccc tatatgtaca 840
taataattaa atgttgaaat ttatgaaata cttttatgaa tttagataat ttttaaatat 900
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tctgttatac tagtgaaaat aaaaatgcac taagggtggg tcgaagtctt gtttgcaact 1140
accaattgtg acagacagag gtttttgtaa gtattttattg tacaattgat gcatgtttat 1200
ttttagcgtt gttattgcct ctggtgtaaa taaatgaaca aatggctatt tgggggaatc 1260
aaaaaaaaa aaaaaaaaaa 1279

```

<210> 374

<211> 190

<212> DNA

<213> Homo sapiens

<400> 374

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tacntttgca aatgtaatgg tggcctgggt gccatccgag aatttgcaga gcacatttgc 60
ctactaatgg aaaagggttaa taattcatgc caaaaataga aattagcgtat atattgagaa 120
aaaaatgata cagcctttctt cagccagttt gcttttattt ttgattaagt taattccatg 180
ttgtaattgtt 190

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<210> 375

<211> 1377

<212> DNA

<213> Homo sapiens

<400> 375

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tcatggccta cacaactagt ggaagtcacat gtttagaaaa taaatggctt gtttaaggaa 60
aagtttttgt gtccaaagct ccttaaagtc agagagattt ctacctggta cttaacatca 120
tatggaaatt gatgcttttag tgagggtggt ggctatccta ttgtcaattt cctgcatcct 180
tttttcttct ttatttttgt atagagacaa ggtctcgcta tgttgcccag gctggtcttg 240
ttcctgggct caagcagtc cccgcctcgt gtctcccaaa gtgcccggat tacagggtgtg 300
agccactgtg cccagcttat ccttttttca ttacacaaaa agactgaatt tggttagtgc 360
taagtgggaa gataaagatg gtatgcacag gaggcccttg ggagccctca gataactttc 420
tcattcttcc aaaatcaggc tgggatgcac tctgtaaatt ttccctgcct aggatgtata 480
cctgaggaat aaggtaagga agatgtcagc aagtcagcct ctggtttacc tgctagctgg 540
catggatcct taaggaagca ggaggaggtt gggaagagag gaagggtgga agttgggtatc 600
ttttaagcgc agagtgtatt taectcagat ttgaaagaat actaaggaat ccagttgttg 660
gggtacatgc tattattaga aggatctaga taatttgtcc tctgagtcac acttgacatt 720
gtacctgttg cacatcaatc cgcactgttt gatactctgg ctgaatctca gctttcacca 780
acattgtcaa aggacctttt ttagtgcca gccatgccta agagtgtgtc atctgaagag 840
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gtaaggtaca aaagtacatg cttggaaaag cagtctgcac caccagtgat aagctgtgac 960
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tttccacttt ctttagtggc attcagacct cctctagttt gacccttacc tccaaactga 1140
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cactagtccac ataggactca tttgaaatat gactagtctc aattgagatg taatgtaagt 1260
gtaaaataca cagcagattt ctaagacagc acacaaaatg taaaatatgt caaaaatatt 1320
tgatactgat tacatgttga aatatatgtg ttgggttaaa taaatgcat taaagtt 1377

```

<210> 376

<211> 489

<212> DNA

<213> Homo sapiens

<400> 376
gacctctgccca tggccctgca gacctgttaca ctgcaactga taccaaagag atcagcactg 60
gaaaagccca atgggtgccac cccggtcttt aatcccactg ttttccactg ccaacaggct 120
ctgactaacc tgcagctccc acagccggca tttatccctg cagggccaat actgtgcatg 180
gcacccgctt caaatattgt gcccatgatg caccgtgcta caccctaccac tgtgtctgca 240
gcaacaacac ctgccaccag cgttccgttc gctgcaccaa ctacaggcaa tcagctgaaa 300
ttctgaacag cagagttagt gagtatcaga atctttccat ggaaacctcc atatggcctt 360
tctatatata ttctcgtatg tcttattcta ccaacacaac aataagcgtg ttgcagtcga 420
tgtattaagc aaagcaaac tgccagccag caaattcaaa taaaaaata aagcattaaa 480
aaaaaaaag 489

<210> 377
<211> 372
<212> DNA
<213> Homo sapiens

<400> 377
cccgattgaa ttctagacct ggggngcctt ttttttcaca ttttaattga atatctacag 60
taggaaggct cttacaatca atgatgtgtc atgggtgtaat ttttttttct ttctccctaa 120
tacataaaat aagtggaaagt tttacaatca ttgggtgtctt aggatcagtg agatacagca 180
tgattttccc cgtgtctcag gcctgcttcc ctgagtcttc caatggcagg aaccacgtgg 240
tggttctcct cagagctctg ggctcagcct ccagaactgg gactgagcta aagagtcact 300
aaatggctac tgagatcagg agcagaattc cctgagagtt gcttatctct gggaaacctga 360
cctgtccaaa tt 372

<210> 378
<211> 558
<212> DNA
<213> Homo sapiens

<400> 378
agaaagagca actttgtttt aactctgcta gatactggaa aacctatgga actaatgaag 60
agcctagggc tttttatttg ttttgagatt gtgccatttc actccagcct gggcaacaag 120
agagaaactt tgtctcacac acaaaaaaag tgtaaatcaa aacattaaaa attaatagtagt 180
ttggaagtag attatcaaaa aggtcctgaa agggagggttc tttggctata atcttttaacg 240
caactctaca ctccctgtat ggagacagat ttctttctag atggttacag tcacaaagta 300
gggttttcag tagcatttag ggatgaatga atcttgcagc acctctccat gtatcttgct 360
agccccctcg aaacttcagg tcagtttagt ctccctcaga aattgttccc cccacaccaa 420
gtttccacat ttacagttat actgatatcc acattgtact gttgtatgtg acacctagat 480
tataggaaat tttggctata gatcagaaat taactgctat gttttgcctt tacgctaaga 540
agattttggt ttgttttagt 558

<210> 379
<211> 993
<212> DNA
<213> Homo sapiens

<400> 379
atttatcaaa tcttatttct tcccactccc ccatttgtac agccacagca tgggaacaa 60
atgggggagt gggagaagaat aagatttgat aaatagttca gggcaacatg atagaagggc 120
atgtacatca tgctaaaaaa aagtgtatgc tttttgtggc aaggaagaac aataaaaaatt 180
tagaaatatt tattaggtgt ctattctgtg ttaataatgt acaataacat tctgggggata 240
atgagctgaa aaaggtatat ggcttcattgt gtatcacagt gcaacaagaa accaatttct 300
gagacagaaa caatttgtaa aggagcacat ttgggtcatgc ctgtaatccc agccttgtcc 360
tcacgtctct cttttccacc ctccctttct ctcaccgttt tcttccactg tcttctctac 420
cacactgtct tctccctgca ctttctcccc actgtcttct tccccacctt tctccccatc 480
ccactttcca aggtctttcc caccctctcc gtccctctct cccctctctc ccgcagtctt 540
ccgggccccca ctgtcttttg cccgcagcca acactgttca gttctgaggt atcggcaggg 600
gcgggggagg cggcagccgt gatggccctg gcagcgactc tctgggtct cctgttggt 660
gttggggagg agctcagggg cccagctcat ggggctgggt gggcgacag acacaccagg 720
cgaggagaca caggcgggg cagcgttga gcgcttctag gtgaaaggca gttggagagc 780
gcgagaaggg ggtgggcaag aagacgatcg gggcgagac ggtggggagt ggaagagggg 840

```

agaagagggt ggggggagag aaaaacgcgg caggaagtcg ctgctgcgag aaggtgggga 900
ggggaagaag atggcggaga ataagaggct ggggaaaaaa gacgatggga gggggagaga 960
agaaagtggg aagaagaatt gaattctata cct 993

```

<210> 380
 <211> 786
 <212> DNA
 <213> Homo sapiens

```

<400> 380
gggaagaaga aagttgagct ttttccctt gagaaacttc tgcatttagt ttctatcttt 60
ccaggcaaaa caaatgggta ttcttttcat acaaccattt tcaaatgaac cttagaaaag 120
tcttaacatt taaggtattt tatgcacaga atacacttag attgatagga aagaactcgt 180
aatggagttt gagtaaagaa aatgactgat gtactaaacc cagtaaaaat tgttgaaaat 240
gttaaaggtc agcatgttct aattgggaat ctagatatag cttagatttc ctattggctt 300
agagtatttg ctataacaaa tgaagtgcaa tgacaattat atattcctac tcggtcatac 360
tggactggct tcgttctctt aatatactca gtaatgactc aagcctctgy ctattaacat 420
accctagtgt ccgtttttta attgccatga gccaaatact tcttgggtata caattgatcc 480
atttatttta atggctgcct tttcattttc atcttttctt gctgctaccc atctatgtat 540
gtagtcatgt gggggaaaat gtagccacat tttttatggg aagactttgt gttaaaagt 600
aacattttga aggtttttta ctggtgaaac tagcctggaa taatgccacc agagactgag 660
tggaaatcgc cccttttgaa ggtgccattc ttatgagcca aaagtttgtc atttaaaagt 720
tcattttgag ggaataacat gtaatatgat ttgaaataaa ggtatggtga agttgacacg 780
caaagt 786

```

<210> 381
 <211> 329
 <212> DNA
 <213> Homo sapiens

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<400> 381
ggcagcgagc ccctgactat actggtagaa tgctgggatg ggcacctgac acccctgag 60
gttgcatccc tggctgacag ggcacacagg gcaagagact ccaatatggt gagggcggca 120
gcagagctgg ccctgagctg cctgcctcac gcccatgcat tgaaacctaa tgagatccag 180
cgggcccctg tgcaagtcaa ggaacaggac aacctgatgt tggagaaggc cgcaattcta 240
acgttactgg ccgaaccgct tgggaataagg ccctgtgctg tttgtctata tgtgattttc 300
caccctattg ccgtcttttg gcaatgtga 329

```

<210> 382
 <211> 364
 <212> DNA
 <213> Homo sapiens

```

<400> 382
gcttgtcaga gcagggattt gcatcacaga ctggccactg caaagacaga tgggaactca 60
caggttttgt gtgtgtgttt gtggttcact gctgatggac gcatgnnaga agccacctga 120
gccttgcccc agccttcctg tggagtgaaa acccagacct gtgtgagcag caggtacttg 180
aagcaagaga agcaaggccg agccaccagg gctttgttag aggtctcttt ctctctggaa 240
accaattgaa caaccaggag ccagaggtct tggtgcccg atgtgggtct aatcctggtt 300
ccatggtctc ccaactgagt gaatgaaaaa aaaaaaaaaa aaaaaattt actgtgtacc 360
cggc 364

```

<210> 383
 <211> 590
 <212> DNA
 <213> Homo sapiens

```

<400> 383
tgttaaatgg agacagtaat agcacagatt aagttgctga gttatgaaga tctgattaga 60
ttatgcatgt gaaagcaata ggccgggccc cctctgcgta atcttatttc taattttaag 120
agccaggaac ccactttttt ggagcctgat gttctaataat tcttctctta cgaaagccag 180
gtcattgctt ttttcactcg cctgatgcac tgtaagagcc ttgtgtgttc tttcaaaagc 240
gatctctcat atttctcgtt ttgggtctt aggtgtcttt tcatttggca atcttctctc 300

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```

tacagagggc tggaaaaact gcagaagacg gcataatccac caccgcgtgc tgggtcggcc 360
ctgcagctgt gtgcacccaa gaactgccaa agaagctggg tcttgccgcg gcggaacgga 420
ccaatcagaa aaagttttgc cctctgcagt ttccgtccgc tctactaggag gcgtgcggc 480
agcgacggcg gcgtcggcgg cgcccggggc tgtcgcgggt tggggcgggt gggctggcag 540
ctgaggtctg tggccatgga gtggggttct gagtccgggt ctgtgaggcg 590

```

<210> 384

<211> 581

<212> DNA

<213> Homo sapiens

<400> 384

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gcattaaatt catttgtttt tataatcagat tcacactctt attttaactt tataatattt 60
actgatatatt agtaggtcta atgtcttttt ctctttttcc ttctcttaaa atatttatct 120
cttcttgccct gtttaacatt tcaaatcaat tttagaacca atttttcaag ttcaaaaaca 180
taagcaaaaa gaaggaaaaa cctcaacgaa accttctggg gtttggattg tgtattattt 240
agggttaagga atatgtgctg ctttagcaaa tgaacttgaa aatcttttat aggcccgggc 300
gcggtgacac atgcctgtaa tcccagatac ttgggaggct gaggcaggag atcgcttgaa 360
ccgggaagca gaggttgac tccagcccg gcgacagagc ggcggcgggt ggggggtggg 420
gggaagcaaa aaacaaatta gctgagtata gtggtgcacc tgtaatccta gctactcagg 480
aggctgaagc acagggattg cttgaacccg ggaggcagag ttgcagttag ccaagatcat 540
gccactgtac tctagcctgg gcaacagagc aagactgtct c 581

```

<210> 385

<211> 502

<212> DNA

<213> Homo sapiens

<400> 385

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ctagtatgaa tgaaaaaaa aaaaaccacc aacatttcat aaacatgact cctgcagcc 60
gatctgtgcc cgacatgggg gtggatccca gaagcgggag acagccttcc acggaactt 120
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<210> 386

<211> 271

<212> DNA

<213> Homo sapiens

<400> 386

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tgcatttaag tcttaacaga agaattgatta ttacacctat gagatttttg tcatataat 180
ggctttgggt gccagtggga atgggtcaa ctcttaagga aagttagacg ccaagccac 240
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<210> 387

<211> 1054

<212> DNA

<213> Homo sapiens

<400> 387

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```

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<210> 388

<211> 366

<212> DNA

<213> Homo sapiens

<400> 388

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gtgtggccga gagctatgac acggagagcg gcttcgagga tgacagagac tgcgacgtag 180
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tcaccagcga ccacctcaag gggctgcatg tcatgggtgc agacattgtc cagatgcaca 300
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<210> 389

<211> 690

<212> DNA

<213> Homo sapiens

<400> 389

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gcatatatgc tgtagagaat gagcatatga atcggctaca gtctcaaaag gcaatgcttc 180
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<210> 390

<211> 1844

<212> DNA

<213> Homo sapiens

<400> 390

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```

<210> 391

<211> 1259

<212> DNA

<213> Homo sapiens

<400> 391

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agtttccctg tacaccactt tctctccttc tatctcaaag ctaattgtaa agtctgcttt 180
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```

<210> 392

<211> 587

<212> DNA

<213> Homo sapiens

<400> 392

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aatataagct cccggaaggc agggatgttg aagtatccca agggcttaaa ggaatgtgtg 540
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<210> 393

<211> 1935

<212> DNA

<213> Homo sapiens

<400> 393

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<210> 394

<211> 357

<212> DNA

<213> Homo sapiens

<400> 394

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gacccagca ggagtgggag ggtctgcaat ggcctcgccc tgtcctgctt tggccagaag 180
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<210> 395

<211> 1201

<212> DNA

<213> Homo sapiens

<400> 395

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<210> 396

<211> 1432

<212> DNA

<213> Homo sapiens

<400> 396

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<210> 397

<211> 439

<212> DNA

<213> Homo sapiens

<400> 397

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cagttgggtg aggggtgttt gcacttgtga cagcagtatg ctgtcttgcc gacggggccc 300

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ttatttacgg gaagcttctg ttcaatccca gcggtcctta ccagaaaaag cctgtgcatg 360
aaaaaaaaaga agttttgttaa ttttatatta ctttttagtt tggatactaa gtatttaaca 420
tatttctgta ttcttcccc 439

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<210> 398

<211> 657

<212> DNA

<213> Homo sapiens

<400> 398

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<210> 399

<211> 1845

<212> DNA

<213> Homo sapiens

<400> 399

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<210> 400

<211> 642

<212> DNA

<213> Homo sapiens

<400> 400

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<210> 401

<211> 1361

<212> DNA

<213> Homo sapiens

<400> 401

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<210> 402

<211> 2547

<212> DNA

<213> Homo sapiens

<400> 402

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<210> 403

<211> 1010

<212> DNA

<213> Homo sapiens

<400> 403

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<210> 404

<211> 946

<212> DNA

<213> Homo sapiens

<400> 404

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<210> 405

<211> 3028

<212> DNA

<213> Homo sapiens

<400> 405

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<210> 406

<211> 329

<212> DNA

<213> Homo sapiens

<400> 406

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<210> 407

<211> 1622

<212> DNA

<213> Homo sapiens

<400> 407

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<210> 408

<211> 1202

<212> DNA

<213> Homo sapiens

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<400> 408
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<210> 409
<211> 425
<212> DNA
<213> Homo sapiens

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<400> 409
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tgttgctgag atcatcgat gcaacagctg ggtaataaga ctacatagc tcaactatc 180
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<210> 410
<211> 907
<212> DNA
<213> Homo sapiens

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tatcgagtcc cataatatcc acttggacat gaagagagac atactccaat ctgcttcatg 420
ccaattcttt ccagagcaaa aaatagtctg ggcttacatg acaaacatcc attgtaatct 480
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cgccggg 907

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<210> 411

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<211> 559
 <212> DNA
 <213> Homo sapiens

<400> 411
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 gtgatgactg acagtgaaga tagtactgtg tccatccaga taaaattaga aaatgaaggc 240
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 cccatggaca tgggtggtgg 559

<210> 412
 <211> 1555
 <212> DNA
 <213> Homo sapiens

<400> 412
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 ttctggacgg cagagcccaa gtttcaagct ttccctgtcc agtggaaaga agactaacct 180
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<210> 413
 <211> 634
 <212> DNA
 <213> Homo sapiens

<400> 413
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 aaatgaaact gtcatgctgt gtcctccccc gcagcagaag atgtgtcctt ccattgagtg 180
 agggttaact tatgtccaca aaggatactt tgagaagacc cctaaggaaac aagcctcagt 240
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 gtatttttaa gcagtagata gaataacaaa ggaatatgaa aaccatggac tgaatggacc 420
 attttatgta ttcagagaga gaagccactc atcattgcca gaaataccat gtaaaaattg 480

gcagttcaga ggttgcaata cttagtatag taaataaata aacgggtcaac attgtgcaac 540
cactacaaaa aagtgtgttg taatgcatca aaaatcaaca caattttatt cactaatgag 600
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<210> 414
<211> 688
<212> DNA
<213> Homo sapiens

<400> 414
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<210> 415
<211> 1156
<212> DNA
<213> Homo sapiens

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attaaattaa aatttc 1156

<210> 416
<211> 569
<212> DNA
<213> Homo sapiens

<400> 416
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gaaatcctga tcttgggaat atctgccttt atcttcttaa tgttaacggg aattctcaa 420

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ctatgtgtta tttatgtaat ctgatacata atctctttca ctgaaatctt gtgatccatt 480
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tttatacaca ctttcttata ctacccatc 569

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<210> 417
<211> 1281
<212> DNA
<213> Homo sapiens

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<400> 417
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ataaacctct gtgtgtttaa g 1281

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<210> 418
<211> 580
<212> DNA
<213> Homo sapiens

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<400> 418
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tattttttaa acatttgaaa ccaagtactg tttaatttca atcagaagat gcaaatatcat 180
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<210> 419
<211> 712
<212> DNA
<213> Homo sapiens

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<400> 419
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gtgtcttatt ctttgtatgt atttcagtga aacaactgaa tatactttat tcttctaat 180
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tacagtttagc tctttccatg gatgtctctt aatttttaag ttcttctctc tttaaacact 420

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atattttgtct cttattttat cactgaattg atgtaaacat tttaaatata attccaatta 480
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taaatgtctt caatcaagat atttgtttgt tctacttaac ctggcacaat attatcaatt 660
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<210> 420

<211> 608

<212> DNA

<213> Homo sapiens

<400> 420

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<210> 421

<211> 2843

<212> DNA

<213> Homo sapiens

<400> 421

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gagtaaacgt ttttccattt gtgcaatgct gatagcaatt gattcctccg cagactcttc 1920
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<210> 422

<211> 382

<212> DNA

<213> Homo sapiens

<400> 422

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<210> 423

<211> 2957

<212> DNA

<213> Homo sapiens

<400> 423

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<210> 424

<211> 1515

<212> DNA

<213> Homo sapiens

<400> 424

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<210> 425

<211> 320

<212> DNA

<213> Homo sapiens

<400> 425

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ttatatcttg agttactaac taaccacgcg tgttggttct atgtgctttt ctttcatttt 240
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<210> 426

<211> 2054

<212> DNA

<213> Homo sapiens

<400> 426

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<210> 427

<211> 571

<212> DNA

<213> Homo sapiens

<400> 427

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aatcactaaa agtactttgc catattggaa cctgaggcaa aaagaaaaat aagtaataat 480

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acattgcatt aaaatattat ttaattgtgga g 571

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<211> 708
<212> DNA
<213> Homo sapiens

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<210> 429
<211> 625
<212> DNA
<213> Homo sapiens

<400> 429
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<210> 430
<211> 2979
<212> DNA
<213> Homo sapiens

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<210> 431

<211> 2299

<212> DNA

<213> Homo sapiens

<400> 431

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<210> 432

<211> 1257

<212> DNA

<213> Homo sapiens

<400> 432

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<210> 433

<211> 893

<212> DNA

<213> Homo sapiens

<400> 433

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tttgttcatt tttatatatta atttctgggg agaggatttg ctgacctctt tattctttca 840
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<210> 434
<211> 807
<212> DNA
<213> Homo sapiens

<400> 434
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ttacaataag gaccccatgg gacagaacat caaaacattc aactttcaag taaatgtctt 720
ggaagtaaac atttaanatt tataggactt cctctggcat gtaggatga tattagaaga 780
gtttcctttg acattgaatt ctgact 807

<210> 435
<211> 442
<212> DNA
<213> Homo sapiens

<400> 435
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<210> 436
<211> 870
<212> DNA
<213> Homo sapiens

<400> 436
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cagtactctg tatgtatcca caaaaggga cttgagaccc acagtatttc ttaatttctg 180
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<210> 437
<211> 655

<212> DNA

<213> Homo sapiens

<400> 437

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tgtgacctga taccagocca gctataaagt attgtatttc tgtagaatat ggaataatag 600
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<210> 438

<211> 814

<212> DNA

<213> Homo sapiens

<400> 438

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gtaataggag acccacaaga aataggtaac atcaaaacgt ttacgacaaa ggtacaccac 180
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cagggcataa ggcaaaactc atcgtgatgg tcatggtagg ggggatcagt gctgactgcc 300
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cgattctcga cgtgaggtgt tcgcgcgaac acttggcccc gcaaacctgc tccccctccg 720
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cactgcccag aaggagagca gcgacggcgg ttct 814

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<210> 439

<211> 450

<212> DNA

<213> Homo sapiens

<400> 439

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caattatgtt aataaataag acaatgctac 450

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<210> 440

<211> 567

<212> DNA

<213> Homo sapiens

<400> 440

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gtgccccctgg atgcgctaac attcactctt gtttgcctcc ggactggcca tgaagtgagg 480
agatgggttat ttaaagagaa ttccctatct atttgacaaa aaatccagtt aatatattaa 540
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<210> 441

<211> 956

<212> DNA

<213> Homo sapiens

<400> 441

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<210> 442

<211> 1804

<212> DNA

<213> Homo sapiens

<400> 442

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gggggtcacc tgtaaactac ttgctaggct gaggcaggat aattgcttga accctatagg 1740
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<210> 443
 <211> 642
 <212> DNA
 <213> Homo sapiens

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<400> 443
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aactatttac tgttaaaaaa tctgtgactt catgaagttg atttttaaag gcagcatcaa 180
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<210> 444
 <211> 2592
 <212> DNA
 <213> Homo sapiens

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<400> 444
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<210> 445

<211> 2092

<212> DNA

<213> Homo sapiens

<400> 445

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<210> 446

<211> 1266

<212> DNA

<213> Homo sapiens

<400> 446

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atgggagaaa cagaaacatg ggagaaagag gtaagggaga cctaggggaa gaaagacaaa 180
ggaaaagagt ttaaagtttg gaggttaact tgccagaggt cacattctgc tagtcataag 240
caattttttt caaagttttt gccttttttt tttgtgtgtg ttgttctctg gctaccttaa 300

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ttcttaagct ttttagaggct cctttctgaa tagaccaag cacacattga aatttctttt 360
tgtgtctgtg tcacaaagac ctgaccatca ctgctttgca ctgtgggac ttgggcaagt 420
gacttaacct ttcagaacct cagttatctc ctctgtaaaa cagataaggg cacctctctc 480
aaacctagggt ggtgaggatt aangagagata atggttaagc acggaacaac ttgcttgcca 540
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<210> 447

<211> 1446

<212> DNA

<213> Homo sapiens

<400> 447

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catggcacac tctgtgtgtc ctttaaaact tacagaggct ggagaaggca gctcatgtct 180
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taataacctg ggaggtgggt actaactgtc ccataattcc ctggatttat atgaaaagcc 360
cagcatttac atttcttctt gttctcactg atttttttta atttttttat ttttctttaa 420
tgcttgggaa aggccaggct cgggtggctca tgcctataat tccagcactt tggagggcca 480
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<210> 448

<211> 697

<212> DNA

<213> Homo sapiens

<400> 448

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tcagtttctt tcttctgtg aacgatgaga cttggagaac gggctgggtc ttcaccactt 120
cctgttggcc ctggcctggc cggggaagg ggcagcgga ccggactgac ctgcagtgc 180
ccgcgatgcc gcgccagcag ggacacttat ggttcattc gagagctgct gccaaaacgc 240
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ccgcgggact gtgttcgtac gtgcatagtt tcgataatc atcgcggggc tgtgttcgta 360
gtgtgctgct ttcatatca caccctctgt gtgcccctt acttctctg tgcagaaagt 420
ataacgtgga aatccacggg accaaatttc tgcagaggcc ttgcccagtg gttccataac 480

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```

tgtagagtct aattgctatc cattacagaa attaatcggt cagttgaaag aagtactgat 540
gactttttcaa aacaaatgaa ccaccgtagc tgacagagaa ccgtatcgta gaggttttga 600
gttagtgctt atttttgcat gttgatgttg actagctaata aaactgtaaa tgtaaaccat 660
gogaataaaaa tgggttttcta tttctcattt cegtgtg 697

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<210> 449

<211> 1354

<212> DNA

<213> Homo sapiens

<400> 449

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cgggactgaa gatggetgaa attccagcaa gcagacagtg gttctctgaa gaggtcccc 60
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ccttctgttc cataagctgc ttcattttct tctccaaat cctctctttg ctgggtggac 180
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tggctaaca tggaatttct atttctattt tcttatgtt aaaagccgga acagcaaat 720
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tgattcagaa gaatgcaacc cttatcaact aggtatatct ctttttctct acatttatgt 1320
tccaaataaa gcaaaatcat gctttcacct gcct 1354

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<210> 450

<211> 1044

<212> DNA

<213> Homo sapiens

<400> 450

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gccgagattg cgcactgca ctgcagcatg gataatggag agagactctg tctcaaaaaa 60
aaaggtaatc ggaacaagaa atttgtcagc taccatatca aaacatctag caggccaggt 120
gtggtggctt gtgcctgtaa acctagcact ttgggaagcc aagggtggag gactgcttga 180
gcacaggagt tcaagaccag tctaagcaac atagccagac tccatctcaa acaacaagaa 240
aaaaacctgt agaatttatt gtttcaagat gtggtagtgg gtaagaccaa tgacttttga 300
atcagtcaaa ccaggctttg agtcctgctt tctgaattat tagctttata ttgtgctggc 360
tacttaactt ctttgaggct cagtttctct atctgcaagg aatgggccct tatcttgggc 420
ccattctttt gtccatcatt ttgtatttac aaactcgtgt gtcacatatt tgttctcgat 480
gctggagcca tatcatatag tgaaaaatgc tataaagaaa aaacataaaa acagagtgat 540
gtcacagagaa taccagtggt gtaatcttgg gagatgatga tgcctgggct gggagctgag 600
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ttttgggttt taagactgct ggagagccag tggcaaggga gtaaaagact catttatggt 840
tttgcttact tgtctgctg ctgtgtgaaa tatgcattgt taagaaatta agagtgaagc 900
ctgggtacagt ggctcacgcc tataatccca gcacttttga aggctgaggc aggtggatca 960
cctgaggtca gaagttcgag accagcctgg ccaatgtggt gagaccccat ctctactaaa 1020
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<210> 451

<211> 1133

<212> DNA

<213> Homo sapiens

<400> 451

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tttactacca ccagccacga aggtaccacg tgtctctgtg ttccaccctc aactgctctg 120
gacagcccac cttggcagcc caacaggtct gccttccctga ccaagctctg tctcaggtgt 180
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ttataatcag gaaaaaccca tgtatatttt attaaaaatt actgtagaaa tgg 1133

```

<210> 452

<211> 1393

<212> DNA

<213> Homo sapiens

<400> 452

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tgttatttct gttttctctg tttcttaggg cgtccacttt tcttctgtcc tttcttcttc 120
gttttaagga gaacagcttt ttctccaata aataagcttt taggatgtcc ttctgcagtt 180
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cttccacagt ccagaaagtg cttctcaatg gcagattctt caactttata agggagatto 480
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<210> 453

<211> 925

<212> DNA

<213> Homo sapiens

<400> 453

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catgcacttt gcaagtgcatt ttgtcttgaa tattttgcaa agatattcta ttgaattgag 60
aggcagcaag tatttgatgt aatgattaca ctgtatcaca caaaaacact tcacagtgcc 120
atggtctggtc ttcatagtag tcagctcttg actttgcttc tgtttttttt tttttctccc 180

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cacaagactg ttagcttttg ctgtggcttc aggagcattt acatgtctta aaagcttata 240
aataatataa aaggctgact gtgttagtag tgcagtagtc agtgcataat gccaaattgg 300
tagtgatgtc tgcacgacat gctgacttga ataagttatt ttcaagttgt ctcatatagg 360
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925

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<210> 454

<211> 553

<212> DNA

<213> Homo sapiens

<400> 454

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catttttttt ttaaacctat aagtactaaa gataaatgag cctgaggcat tcttttatct 120
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ctgcaccgtg acaatttctt tatcctctcc aaactcaaaa ctctcaccaa ttattactat 420
tttagggcca aagttaaggc aaagaaccca agaaagataa ttacggggaa acaaaaacaa 480
tggcaagtta aaaatgattt acaaatattt aaaacttctt taaaaaccac ctaaaacttc 540
ataagcaaaagg
553

```

<210> 455

<211> 1233

<212> DNA

<213> Homo sapiens

<400> 455

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tgattgaaga agagaaaaata tctgattgtt ggcctcatag aaattttgtg tagctaaagt 120
atttgcattc taaatctttc aaatggagaa attgagggtta agcaaaaaata ggtgatggga 180
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<210> 456

<211> 1393

<212> DNA

<213> Homo sapiens

<400> 456

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<210> 457

<211> 471

<212> DNA

<213> Homo sapiens

<400> 457

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<210> 458

<211> 1429

<212> DNA

<213> Homo sapiens

<400> 458

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<210> 459

<211> 1743

<212> DNA

<213> Homo sapiens

<400> 459

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<210> 460

<211> 2135

<212> DNA

<213> Homo sapiens

<400> 460

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<210> 461

<211> 1226

<212> DNA

<213> Homo sapiens

<400> 461

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<210> 462

<211> 970

<212> DNA

<213> Homo sapiens

<400> 462

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<210> 463

<211> 563

<212> DNA

<213> Homo sapiens

<400> 463

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<210> 464

<211> 1138

<212> DNA

<213> Homo sapiens

<400> 464

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<210> 465

<211> 775

<212> DNA

<213> Homo sapiens

<400> 465

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<210> 466

<211> 1636

<212> DNA

<213> Homo sapiens

<400> 466

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<210> 467

<211> 1422

<212> DNA

<213> Homo sapiens

<400> 467

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<210> 468

<211> 1727

<212> DNA

<213> Homo sapiens

<400> 468

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<210> 469

<211> 2532

<212> DNA

<213> Homo sapiens

<400> 469

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<210> 470

<211> 1088

<212> DNA

<213> Homo sapiens

<400> 470

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```

```

cctaaataaa aagattgtat tgatacagag acattggaga aggagatttt aaggcagttc 1020
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<210> 471
<211> 635
<212> DNA
<213> Homo sapiens

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<400> 471
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acagggttaga gttggggacc cctgttggcc acttgttgac ctctcatagt ggtgcttggg 180
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atgttttcag gggatgccca ttgtcccaa gcttatcctg taattctaga attacctggg 540
gtcctgatgc attttccact agaggttgct aatcagcatg ttttagccca agtccgcctt 600
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<210> 472
<211> 408
<212> DNA
<213> Homo sapiens

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<400> 472
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gctctgggtc ctctttaagt ggtaatgctt cataccaact tcccaaagt agcctgggtg 360
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```

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<210> 473
<211> 828
<212> DNA
<213> Homo sapiens

```

```

<400> 473
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<210> 474
<211> 2417
<212> DNA
<213> Homo sapiens

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<400> 474

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<210> 475
<211> 1087
<212> DNA
<213> Homo sapiens

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```

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gcagggtcagt tgtaataaat ctaggatgtg atgatgacta tgtaatttga ttttctgaaa 1020
tcagaccctg agaggggaaa atcttaaagt aaattacatt aaattatctg tgcatttcac 1080
accaggg 1087
```

```
<210> 476
<211> 504
<212> DNA
<213> Homo sapiens
```

```
<400> 476
catttggcctt tttaccatgt tcttcccttt ctttttcccg cttccttaat gtaattttaa 60
ccctggcaaa cattcttttag aaaccaagag gaaagaaaga acaaataatca aaaaagacat 120
agaatttaat attgatacaa tttcacctct aaaatggatt tgaagaaatg caactttata 180
tcaaaaaatg tcatctgatt tcttttgttt cttttttaa ttaagtatac agatgatttt 240
atgttttttt tcaggggagc ggaatatttg tttcttttac ttgttgtttt cagttttctc 300
tgccattcat gtttcttttt tgtgttcagt gtttcaaata caatttgtat ttaaggatttt 360
taaaatacca aactgtaact gagtacagt ggatcggttt ctgttaggat gttaatatta 420
tacaatgaaa tctataaagt gttgtcaatt tgattattga cacatataac atgtttacaa 480
ataaactgtg gtattgatca agtt 504
```

```
<210> 477
<211> 404
<212> DNA
<213> Homo sapiens
```

```
<400> 477
gcatgatttt atttaaaatg tgtccaataa gacttgccac ttggaatgaa catttttact 60
tctttctca tattattaga aacagtattt cctcatttca tggagtttct tagaaaagttc 120
taagtattaa cagaagagaa aatgaaacc gtggggagat taaataacag gaagtttaca 180
ccacagcaag ggtgctcacc catcccaatt tcgggggaca cacaagtgc tattgggtga 240
aatagaccag atcatgcaaa tcatcgtatg atcacttggt atcctttggc agttctgaca 300
ttcattgtca ctgacacaga tattaaaatg agtcagatga ctgcagtga tgggaaatca 360
tcttttgcct ttggtggtgg agagaagact aggaacacaa aggc 404
```

```
<210> 478
<211> 2525
<212> DNA
<213> Homo sapiens
```

```
<400> 478
tttttttttt gaattcagtc aagtttatta aacttgcgtg gtgctcagca ccgccctagg 60
cagtaacatg aaaaacatta caaagaaga tctcaacaag ggaaaaatat attctgtact 120
atattaattt ccaattcatt acatgttgct ttttaagtg ttcttaggtc actttggggg 180
atgttggtct cttctttctc catgttcccc taaagcttcc aactgttga attatgtgcc 240
tgtggcgacc atcctccagg aagggcacct tctgctgat gaggcaacca tgggttggtc 300
agggctgggg tccgtgggtg gaggagacat gctgagagaa aaaccatcaa ccccgagagc 360
tcaggacact cacagtgaat ccagaaggc caaacgtggg gaagcccaa agagggctct 420
gggccccctc ctcacccctt cccctagggg atgtgcttaa agtgctaacg ccgtaggaaa 480
atgatgcata gctacaagcc gtccctgggtg ctactagact catcgctgc ctcttctcc 540
ctaaactgtg ctaatactgg gcgatggcac aggcctaag aaaagtctag tgcccagtga 600
agtagtagag aaggtccaac gtgtaacct gaattcccaa gaggaggtgg gacagaagag 660
aagaagtga gggcagagac gtgtgcagca aaaaggacgt ttgtgcttgg ccggtaccgc 720
tgggtcaggg gttggtttct gtgcaagggt caattgggt ctgcacagct agcaggggtc 780
taaaatttac ctgagggaa aaggctacat agcataggaa ggaggaaaat ccatgcaggg 840
ccctccctgt ccccccacac ggcacgcccc catgcctact gtacaagggt ctgtggagta 900
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ttacagccca gtgaaatgca tcacgtgcat gacatggagg gcacccagc caggagggca 1140
agcaaaagtg gcagtggcat aacttcttca cgttggtgac ctagttaggt agaggatgcc 1200
ttggagggaat gggagggtgt ccagaggcca agagaatact cctgtctcgc cctcgggtca 1260
gagccagatg tcatcactgc tcacgtgga cactcgatag atatagccca gcactgggag 1320
gcggatgaaa ccttggctgg tgaggaggcc gccgggtctc gggtcagaa gctctggccg 1380
gctgtgttct tgagccatct gccgtctgc ttgtttcact gctctggaat ctggagttag 1440
```

```

gtcattgagc tgaaggttg acgggaggga catgttctcc cgtggcaggc gcacgttggt 1500
gagttttagg ttgttgaggt cacttgatat cagagatggg tgccgggagg ggcctttggt 1560
tttcttctct tttctgcaga ccaggcaggc caccaagggt ctgaaccca cgagggtgcc 1620
cagtgcagac ccagcagcca caacaatgcc cagcagtgcc acttccaccc gggtagccag 1680
aagccctggg gctggaagcg acgcactggt gacacccacg tcattggtgg ccaccaccga 1740
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gttctgcgca tccagcacca ggaagtgcga ggtgttgaca gtcactggcc catcctggtc 1860
gatccagggt acattggccc gcgggttgcc acgcaccagg gcaaacagga caaccaggag 1920
gcctggggccc tgagcttcct ggtacttgcc gccgacttgg gcaatctctg gcttgaattg 1980
cacattaagg atgacagagg cgttggtgta tgggccactt ctgggggtcc gcagagagca 2040
gttgagctca tgcctggccc gatgggcagt gacagtgaag gtgctgggtc ctccagagaa 2100
ggcctccccc cccacgctca gcagtcttga ggtgctggcc tcctgcagct gtccatccag 2160
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cccccaacct gagctcagaa gggctggcag gagcagcagt gtgtgccgga gggcggtctg 2340
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agcgcgcggc gagcaactgc tcagggtctg taggcaccgc agtccgctgc aggggcgggg 2460
gctgcgcagc gcggggccaa tcgatgccc accacggggc cgaggggccc ttaccgggca 2520
ggtgg 2525

```

<210> 479

<211> 544

<212> DNA

<213> Homo sapiens

<400> 479

```

aagaaataga agaactcacc aagatttctg acgaactgat tgccaaaatg gggaaaagct 60
aactctgaac cgaatgtttt ggacttaact gttgcgtgca atatgaccgt cggcacactg 120
ctgttctctc agttccatgg acaggttctg ttttcacttt ttcgtatgca ctactgtatt 180
tcctttctaa ataaaattga ttgtattgta tgcagtacta aggagactat cagaatttct 240
tgctattggt ttgcattttc ctagtataat tcatagcaag ttgacctcag agttcctgta 300
tcagggagat tgtctgattc tctaataaaa gacacattgc tgaccttggc ctctgcccct 360
gtacacaaat tcccagggtg agcagctttt ggatttaata tgaacatgta cagcgtgcat 420
agggactctt gccttaagga gtgtaaaact gatctgcatt tgctgatttg tttttaaaaa 480
aacaagaaat gcattgtttc aataaaattc tctattgtaa ataaaatttt ttctttggat 540
cttg 544

```

<210> 480

<211> 543

<212> DNA

<213> Homo sapiens

<400> 480

```

gaggggtgct cctgatgccc cgggtgcagg gcgggcacca gcgagcgaga cccaaggggc 60
ctagaaccca ggagcgcaaa ccaccgttag ggcctgaggg acgcagaggc gggtaggagta 120
gtgtttctca gattcgtggg aggcgcaggc gcgccagcaga agcaattttc ctcccctgag 180
caatgctagt tctcctcagg ccaggatctt ccaactaacgt gtccttccac ctctccacag 240
gactccaagc tgctgtcccc tctctgccgc atctgaggct gggaaaactt cctaggagaa 300
ggcaagagaa agccaccaga ccagagccga ggactaaact ttaaggtcga agacggcaga 360
ggggcagggt cteccctgca caccacaagg cctctcctgc acccgcgagg ccttccctga 420
gcgcccaggc ccccgaaatg cctgcctccc ttctgacaaa aggggggggt aggatgtgaa 480
ggggtagtgc aaccaataat gtttttgtaa acacaacaac agggaaatac atggaggaaa 540
tct 543

```

<210> 481

<211> 482

<212> DNA

<213> Homo sapiens

<400> 481

```

cgcgcggagg cggaggcttg ggtgcgttca agattcaact tcacccgtaa cccaccgcca 60
tgcccgaaag aggcattgct gctggagggt taatggacgt taatactgct ttacaagagg 120
ttctgaagac tgccctcatc cacgatggcc tagcacgtgg aattcgcgaa gctgccaaag 180

```

```

ccttagacaa ggcgaagcc catctttgtg tgcttgcatc caactgtgat gagcctatgt 240
atgtcaagtt ggtggaggcc ctttgtgctg aacaccaaat caacctaat aagggttgatg 300
acaacaagaa actaggagaa tgggtaggcc tttgtaaaat tgacagagag gggaaacccc 360
gtaagtggtg tgggtgcagt tgtgtagtag ttaaggacta tggcaaggag tctcaggcca 420
aggatgtcat tgaagagtat ttcaaatgca agaaatgaag aaataaatct ttggctctcc 480
nn 482

```

<210> 482

<211> 852

<212> DNA

<213> Homo sapiens

<400> 482

```

gattaattgc tttatagtac aggtaaactt tgagaataag actatgtttc aaaaacagta 60
agtcocaaat aacaataact cgtgcattaa tggagcgcat tccctggttt tagttcacct 120
tgcttatacc tgatgacttg gtttctaatt cattatgcga gtcagtgagc acctttaagg 180
gtttatgaca gtcactataat tgccttggtc agggccaaag gacttggtta tatgcttttc 240
ataccaaaat gacataattt cattgaggaa tctgcttatt aaccattcc cctaaaaatg 300
cccaagttaa atataaagaa tttttctctc ctctctaact tgaagttaca ttgcaacatg 360
taactctaag acttaaatct cagtgaagtc tccctggcat cttcttgggc cctcaagggtg 420
acacctgtgt caagctgtac tctgtgtagt ataggtgacc ctctttctca aggaccggac 480
atgccaaaaa ggtttccctg cccaaaagca taaccaaca aggagcatct ggggaagggga 540
ctccttgctc caaccocaaat tattcatttg acaaggaaact gtctatcacc tactctgccc 600
tagccctgtg ctagggtgctg tgggcaactg agtgaacaac aaaaactaat aacacttgac 660
cacattgaat gtaccggatc attcattgaa tgatcactaa tggagagtta caaagcaatg 720
gggtctgaag gaaagggtaca ggggttctatg agggaaatag ccaaggagcc tgatgcagac 780
tgggggctga gggacagctt cctgaggta atgtgacttg ggctgaacac ttaagaaagt 840
ggtgaaaact tt 852

```

<210> 483

<211> 955

<212> DNA

<213> Homo sapiens

<400> 483

```

gaatagctcg atgatctgac ttggttctcg tacgggtccag tttgtacata aacatttttg 60
tccataggga cagtgaagtg tactgatgca ggttgagagc tacaatggca ctatccaaaa 120
acaaaacgaa aaacctaca tggagcttgc tccctgctg cattatgcag agatgggtct 180
caccocgttc tttcatgtga gaataagcac cttattcatt atagaaacat tgtgggtgtt 240
tccctgtact cattgctgaa tgcagtcctc cagtttattt tgaattatgt ttgagtacat 300
atgattacaa acaatataca tgcctcctc aaacaaaagt tctctacaca tttcttagaa 360
atatatacag tatgcaagca acttgcatc tgcctggtga gttttgtatt tattgagaat 420
atatattaaa atatcccat ccaatcatgg atccgataaa ctttataatt aagctatttg 480
tccaacattg tgagtcataa ttactgtgag cttacaactt caggcctttt tttcctcata 540
aattttagtt ttcattgctt tttgattaca acttttatga tgatagtagt ttttcataatg 600
cataatacca aaagtcacaa catgttggtga gtgatttctt tccaaggact atcaggggacg 660
tccctgttgt caagcagggg gtaataaatt gtggtaataa atactaccac aggcggggcg 720
cgggtggtca cctgttaatc ccagcatttt gggaggccaa tgcgggcaga tcaacttgagg 780
ccaggaattg gagaccagcc tggacaacat agcaacaccc tgtctctact aaaaatacaa 840
aaattggcct ggtgtggtgg tgcacatctg taatcccagc tacttgggag tggagggtgc 900
agtgaagcaa gcacgccact gcactccagc ctgggcaaca gagtgaagct ctctc 955

```

<210> 484

<211> 488

<212> DNA

<213> Homo sapiens

<400> 484

```

aggagtttta agtatgttaa aaatctatac tggacagtta caagaaatta ccggagaaaa 60
gcttgtgagc tcaccaaaca aggatttcag ttagatcttt gtctttcttg aacttaaaaga 120
aacaatgac aaagtgtgaa tggaaaagcc tgctgttgtt ccacatctcg ttgctgttta 180
cattcctttg tggagcctac atcttcttaa gcttttttagc aggtatatgt tgaacacttc 240
tglttcatgg ttgagacaga atcagaggcc atggatactg acaactgatt tgtctgtttt 300

```

```

ttttctctgt ctttttccat gactcttata tactgcctca tcttgattta taagcaaaac 360
ctggaaaaacc tacaaaaataa gtgttggtgt ttatctagaa aaatatggaa aatatgtctg 420
ttattttttgg tgaagaaaat caattttgta tagtttattt caatctaaat aaaatgtgaa 480
ttttgttt                                     488

```

<210> 485

<211> 801

<212> DNA

<213> Homo sapiens

<400> 485

```

gagcccccg agctgctacc gtggcgggcg cgctgtgagg agcagccagg gggaggcagc 60
tgccgctcgc cgggtgagtat ccgggaagcg ccaccatggg gctccgtaag aagagcacca 120
agaaccccc cggtctcagc caggaattca tccctgcagaa tcatgaggac atcgtctcct 180
gcgtggggat gttcttccctg ctggggccttg tgttcgaggg aacagcagaa gcatccatcg 240
tgtttctcac tcttcagcac agtggtgctg tccctgcagc agaggaacaa gccacgggct 300
caaagtcctt ctattattat ggtgtcaaag atttggccac ggttttcttc tacatgctgg 360
tggcaatcat tattcatgcc acaattcagg aatatgtgtt ggataaaatt aacaagagaa 420
tgcagttcac caaagcgaaa caaaacaagt ttaacgagtc tggtcagttt agtgtgttct 480
acttttttct ttgtatttgg ggcacattca ttttaatctc tgaaaactgc ctgtcagacc 540
caactcttat atggaaggct cgtcccatata gcatgatgac atttcaaata aagtttttct 600
acataacca gttggcttac tgggttcctg cttttcctga actctacttc cagaaaacca 660
aaaaacaaga catccctcgt caacttgctt acattggctt tcacctcttc cacattactg 720
gagcttatct cttgtacttg aatcatttgg gacttcttct tttggtactg cattattttg 780
ttgaattact ttccacatg t                                     801

```

<210> 486

<211> 668

<212> DNA

<213> Homo sapiens

<400> 486

```

atgagaccac cctgactaac atggagagac cctgtctcta ctaaaagtac agaattagcc 60
gggcgtgggt gcgcattgcc ataattccag ctactgagga gacttgaggt aggagaatca 120
cttgaacctc agcggcggag gttgcagtga gtcgagatcg cgccagtgca ctccagcctg 180
ggcaagaaga gcgaactcgg gtctcaagtt aaaaaaagaa agcaaggaaa gagtaattta 240
caacgaagga aaaaaaccca cagcacaccc ttccggctg tccagcgtct cctgatgtca 300
cagtggctgc gtgtccttgg ggtgggtgag gtgtggggag cccagccctt ggccctgcct 360
cccgcgcccc gctccccctt tctctcttac tccggttaag catagcagg cctccgctcg 420
tttcagatat gaatttgttt tatagattat aaatatgcat atacagtgtg tgtataaagc 480
agaatgcctg cctttcctgg ttattttttg taccatattg taaattatat tattttattc 540
ttaccaattt tgggaataaa aggtgttttg gttatttaat ataataagag ctgttaaaact 600
tctgtttaaa ttccagttc aacttgtaaa tgtttttatt gtgcataaat acataactaat 660
gttgatct                                     668

```

<210> 487

<211> 852

<212> DNA

<213> Homo sapiens

<400> 487

```

aatcatatga atcatttagt gttaatgttt gaaaaagctc ttgcaatcaa atctgtgatg 60
tattaataat gccttatata ttgtttgtag tcattttaag tagcatgagc catgtccctg 120
tagtcggtag ggggcagtct tgctttattc atcctccatc tcaaaatgaa cttggaattta 180
aatattgtaa gatattgata atgctggcca ttttaaaggg gttttctcaa aagttaaact 240
tttgttatga ctgtgttttt gcacataatc catatttgct gttcaagtta atctagaaat 300
ttattcaatt ctgtatgaac acctgggaag caaaatcata gtgcaaaaat acatttaagg 360
tgtgggtcaa aataagtcct taattggtaa ataataagca ttaatttttt atagcctgta 420
ttcacaattc tgcggtacct tattgtacct aaggggatcc taaagggtgg ttgtcactgg 480
tataaaacag aaagcactag ggatacaaat gaagcttaat tactaaaatg taattcttga 540
cactctttct ataatttagc ttcttcaacc ccacccccac cccaccccc cttattttcc 600
ttttgtctcc tgggtattag gccaaagtct gggagtaagg agaggattag gtacttagga 660
gcaaagaaag aagtagcttg ggaacttttg agatgatccc taacatactg tactacttgc 720

```

ttttacaatg tgtagcaga aaccagtggg ttataatgta gaatgatgtg cttttctgccc 780
 aagtggtaat tcactcttggg ttgctatggt aaaactgtaa atacaacaga acattaataa 840
 atatctctag ag 852

<210> 488

<211> 367

<212> DNA

<213> Homo sapiens

<400> 488

cggacggaga gcgcgaggac tcggcgggctg agcgcgcccc acagcagcta gaggcgctgc 60
 tcaacaagac tatgcgcatt cgcacgacag atggacggac actggtcggc tgctttctct 120
 gcactgaccg tgactgcaat gtcacctctg gctcggcgca ggagttcctc aagccgtcgg 180
 gtcagtggcc ggggaatgca caccgcctg attcctctc tgccggggag ccccggtgctc 240
 tgggcctggc catgggtacc ggacaccaca tcgtttccat tgaggtgcag agggagagtc 300
 tgaccgggac tccgtatctc tgaccacgat ggcgcttacc ttccagactt cattaactt 360
 atgaccg 367

<210> 489

<211> 1436

<212> DNA

<213> Homo sapiens

<400> 489

ggggaggcgg aggcaccaac taagagcgac ctacgcatcg aaagccgccc tcgggggctc 60
 atggcgggac gctcctggga aaggctttag ccgcggtgtc tctctctctg gccttggcct 120
 ctgtgactat caggctcctc cgctgcccgc gcaccaggc gttcagaaac tcgttttcat 180
 cttcttggtt tcactctaat accaactgca tctctggttc taatgggttc aaagaaaatt 240
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 ctaatgagaa agtgggctgg cttgttgagt ggcaagacta taagcctgtg gaatacactg 360
 cagtctctgt cttggctgga cccagggtgg cagatcctca gatcagtga agtaattttt 420
 ctcccaagtt taacgaaaag gatgggcatg ttgagagaaa gagcaagaat ggctgtgatg 480
 agattgaaaa tgggaagacc agaaatcctg caggacggac tggactggtg ggcggggggc 540
 ttttggggcg atggggccca aatcacctg cagatcccat tataaccaga tggaaaaggc 600
 atagcagtgg aaataaaatc atgcactcgt tttctgggaa gcatactcta caatttggtg 660
 caataaaaag gaaagactgt ggagaatggg caatcccagg ggggatgggt gatccaggag 720
 agaagattag tgccacactg aaaagagaat ttggtgagga agctctcaac tccttacaga 780
 aaaccagtgc tgagaagaga gaaatagagg aaaagtgc caactcttc agccaagacc 840
 acctagtgat atataaggga tatgttgatg atcctcgaaa cactgataat gcatggatgg 900
 agacagaagc tgtgaactac catgacgaaa cagggtgagt aatggataat cttatgctag 960
 aagctggaga tgaatgctga aaagtgaat ggggtgacat caatgataaa ctgaagcttt 1020
 atgccagtca ctctcaattc atcaaaactg tggctgagaa acgagatgca cactggagcg 1080
 aggaactctga agctgactgc catgcgttgt agctgatggg ctccgtgtaa gccaaaggcc 1140
 cacagaggag catatactga aaagaaggcn gtatcacaga atttatacta taaaaggggc 1200
 cgggtaggcc acttggccta tttactttca aaacaatttg catttagagt gtttcgcac 1260
 agaataacat gagtaagatg aactggaaca caaaatttgc agctctttgg tcaaaaggaa 1320
 tataagtaat catattttgt atgtattcga tttaagcatg gcttaaatca aatttaaca 1380
 actaatgctc tttgaagaat cataatcaga ataaagataa attcttgatc agctat 1436

<210> 490

<211> 1460

<212> DNA

<213> Homo sapiens

<400> 490

aaatctctct catggctcat gttcacttcc cttttcaagt tgaagaggtt tcttttttgg 60
 tgaccactat ggtatatggt gggcaatgcc ctgccagtc caacggtaga gaaaaatagg 120
 ccgtccccc caactctaca attaacatca gaggaatttt tttaacagtt catcttacta 180
 tcaactttta aaaagagaaa catctgtttg aaaatattct ctgtgatgat ttcttaatt 240
 cacttttgaat tcagtttctt actatgaagt cattaatgta agaacttggc caacaaagct 300
 tttcttctca taggctggct ctactagggg aactagtgtt tggtaaaactg ctgggactac 360
 cacaatggga ggggtacagg tataaaatta agttatctta aaatgtttca gcaatgatgc 420
 acgtaggaga ccataatagg tgggtggtaaa tgttttggcc ccgtatagga atgattttaa 480

```

ctaagacgta tgctattccc tatgcaacaa attatcaaac aggatatgtc ttgtgacctg 540
tttttttttt taaggacaca tttttaatag ctgaaaatct ctgataatga attagagtgt 600
gtagttaaaaca tgagaattag ttattattatc ttatttttaa aattcaagac taagaacttc 660
agagaatgaa gagtctatta aaatgaggtt catcttaatg ataggcaaac caaactcata 720
ctgcttgaca tgttttgaaa actggtaata ttgagggtgt acagcacatg tacttaaaaa 780
tgacactgga ctatcttttg ctctgagcca tgccacttac cgaaattgta aatacatttt 840
tcacaaatgc attgccaatt attaccatcc ctcaaagcaa taaattgtga cagttgcttt 900
aaatgtttgt cagcaactgt tttcatttgt tcagatattt tgaatagcta cactaataac 960
tggtattatt tgggtgaacat aaaaaataa atagatctgt atattgatgg tagactctcc 1020
atattgaaat gattattttc caaacatttt cattttggtc aataattcaa actaccactt 1080
aggcaaaagta ttcgaaacact gtgtcctttg ttttaaggaaa tataaaaaaa aatcaccttt 1140
ctttttgtgc aaaaaaataa ttatttcaat cacatttcag aaccgccagg gcaagaaagt 1200
ataaagcagg atcatgttaa gaaaaagaa aaaaagatca tgagtcactt aatatgtat 1260
ttttatttgt aacaaacaag tattaactg taaagtattt ttgtacaaat ttaatacttt 1320
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<210> 491

<211> 2614

<212> DNA

<213> Homo sapiens

<400> 491

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cagtagtggt tggggccctc ccctcaggct ccatttttaa taagttttta gtatttttgt 2520
taagtgtagg cattgagctg ttgggttttg tatattattt atatagagac ccagagctg 2580
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<210> 492

<211> 587

<212> DNA

<213> Homo sapiens

<400> 492

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<210> 493

<211> 772

<212> DNA

<213> Homo sapiens

<400> 493

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<210> 494

<211> 705

<212> DNA

<213> Homo sapiens

<400> 494

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<210> 495

<211> 426
 <212> DNA
 <213> Homo sapiens

<400> 495
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 ttacagtcga gctacttctc atctgggtgat atttattcat ggaacatgaa ttttaagata 180
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 cttctcttca tttctacttt tttttttcat tctcttccca agtagcata tcttcagacc 360
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 cttttt 426

<210> 496
 <211> 957
 <212> DNA
 <213> Homo sapiens

<400> 496
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<210> 497
 <211> 1342
 <212> DNA
 <213> Homo sapiens

<400> 497
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<210> 498
 <211> 1556
 <212> DNA
 <213> Homo sapiens

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<400> 498
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<210> 499
 <211> 772
 <212> DNA
 <213> Homo sapiens

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<400> 499
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<210> 500
 <211> 650
 <212> DNA
 <213> Homo sapiens

<400> 500

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<210> 501

<211> 6274

<212> DNA

<213> Homo sapiens

<400> 501

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<210> 502
<211> 1837
<212> DNA

<213> Homo sapiens

<400> 502

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tgtagctgct gcttcaataa aaacaaaatt atattcg 1837

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<210> 503

<211> 435

<212> DNA

<213> Homo sapiens

<400> 503

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gctgagtgag tataaacatt actactattt catcttagct aacaagtgtc atttacttat 360
gtttcttatt tagtggacag aatctatcca aatgactaaa atttagtcca gattaaaaca 420
accaattatc catct 435

```

<210> 504

<211> 937

<212> DNA

<213> Homo sapiens

<400> 504

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cactgccttt gctgtatccc agaggtttga taggtcgtgt cactattatt cagttcaaat 180
aatttttaat ttcatctttg atttcattgt tgaccaaatg atcatttggg agcaggctat 240
ttaattccca tgtatttga ggggttcaag ggtttctttt ggagttgatt tccagtttta 300
ttccactgtg gctcgagaga gtacttgcca taattacgat ttctttatat ttgttgagac 360
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<210> 505

<211> 476

<212> DNA

<213> Homo sapiens

<400> 505

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tgactgtgc cagatgcctc aggaggagaa cctccccag tgactgtga aggatgacac 180
agcatttctt cctaatagaca cgcgaccgtc ctggtgcctc tacatggttg atgcgggcag 240
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agactggccc accctgccta cttccctact gacaagttct ttggtatttc aaaagggaga 420
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```

<210> 506

<211> 1073

<212> DNA

<213> Homo sapiens

<400> 506

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<210> 507

<211> 857

<212> DNA

<213> Homo sapiens

<400> 507

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gttttcaaaag ctatccagga aaaataaaag atgtctaaca ggaaatcata caagtccttg 180
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ccaaaacact ataataat ttttggacaa gtatacattt ctgttttaaa gaaatgtatg 360
cttttatttt gtatatatta taatttaaat gtatacattt attttgcaca ttgttaatgt 420

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```

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aatttgaatt acagaaaagc attggtttaa ataaatcctc aaaaaagtaa tcccagggtca 840
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```

<210> 508

<211> 569

<212> DNA

<213> Homo sapiens

<400> 508

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<210> 509

<211> 586

<212> DNA

<213> Homo sapiens

<400> 509

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tgtgtgaagt ttttatcaaa ctgtaatat tgtgaatgga atgccttgca atatgaatgt 540
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<210> 510

<211> 2399

<212> DNA

<213> Homo sapiens

<400> 510

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<210> 511
 <211> 1061
 <212> DNA
 <213> Homo sapiens

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<400> 511
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<210> 512
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 <212> DNA
 <213> Homo sapiens

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<210> 513

<211> 1087

<212> DNA

<213> Homo sapiens

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<210> 514

<211> 1116

<212> DNA

<213> Homo sapiens

<400> 514

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<210> 515

<211> 2082

<212> DNA
<213> Homo sapiens

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<210> 516
<211> 578
<212> DNA
<213> Homo sapiens

<400> 516
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<210> 517
<211> 486
<212> DNA
<213> Homo sapiens

<400> 517

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<210> 518

<211> 1433

<212> DNA

<213> Homo sapiens

<400> 518

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<210> 519

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<212> DNA

<213> Homo sapiens

<400> 519

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 <212> DNA
 <213> Homo sapiens

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<210> 521
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 <212> DNA
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 <211> 2269
 <212> DNA
 <213> Homo sapiens

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<210> 523

<211> 903

<212> DNA

<213> Homo sapiens

<400> 523

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<210> 524

<211> 490

<212> DNA

<213> Homo sapiens

<400> 524

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<210> 525

<211> 1307

<212> DNA

<213> Homo sapiens

<400> 525

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<210> 526

<211> 2010

<212> DNA

<213> Homo sapiens

<400> 526

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<210> 527

<211> 651

<212> DNA

<213> Homo sapiens

<400> 527

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tgagccgatt atctgcaatt atgaaatgaa gtaactcaag atgagcaagt taaaagtgat 240
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caaagggtgt tcacaaatat tgttgcagtt acttatgaat gccagcaaag aatctcccc 600
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<210> 528

<211> 539

<212> DNA

<213> Homo sapiens

<400> 528

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<210> 529

<211> 661

<212> DNA

<213> Homo sapiens

<400> 529

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catccttttg gagtgtcttg ttccctcgtc atagttcagc actgtgacca cettgggggtt 600
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<210> 530
 <211> 363
 <212> DNA
 <213> Homo sapiens

<400> 530
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 aaaattaata ttgatgccta ccttcatcaa acaacaacaa caaaaaatca gttccaagat 180
 ggactagaga ttcaaatggt aaaagccaaa caataaagct tttagaagaa aacataggat 240
 actctcttcc tgccttagga tagaaaagga acttacacaa gatacaaaaa ctgctaacca 300
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<210> 531
 <211> 673
 <212> DNA
 <213> Homo sapiens

<400> 531
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<210> 532
 <211> 317
 <212> DNA
 <213> Homo sapiens

<400> 532
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 gaccgagact cgtctt 317

<210> 533
 <211> 1193
 <212> DNA
 <213> Homo sapiens

<400> 533
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<210> 534

<211> 2229

<212> DNA

<213> Homo sapiens

<400> 534

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<210> 535

<211> 573

<212> DNA

<213> Homo sapiens

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 <211> 470
 <212> DNA
 <213> Homo sapiens

<400> 536
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<210> 537
 <211> 316
 <212> DNA
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<400> 537
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 aatctttcat ttctctatgt atgctttttt ccttttttgc ccagtttctt tctacttgc 240
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<210> 538
 <211> 1850
 <212> DNA
 <213> Homo sapiens

<400> 538
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<210> 539

<211> 2083

<212> DNA

<213> Homo sapiens

<400> 539

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<210> 540

<211> 1319

<212> DNA

<213> Homo sapiens

<400> 540

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<210> 541

<211> 1715

<212> DNA

<213> Homo sapiens

<400> 541

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<210> 542

<211> 350

<212> DNA

<213> Homo sapiens

<400> 542

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<210> 543

<211> 676

<212> DNA

<213> Homo sapiens

<400> 543

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<210> 544

<211> 605

<212> DNA

<213> Homo sapiens

<400> 544

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<210> 545

<211> 477

<212> DNA

<213> Homo sapiens

<400> 545

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<210> 546

<211> 970
 <212> DNA
 <213> Homo sapiens

<400> 546
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<210> 547
 <211> 1303
 <212> DNA
 <213> Homo sapiens

<400> 547
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<210> 548
 <211> 444
 <212> DNA
 <213> Homo sapiens

<400> 548
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ccaagcattg gggccgccaat cctgcctggc actggctgat gggcacctct gttgggtcca 360
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<210> 549
 <211> 779
 <212> DNA
 <213> Homo sapiens

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<400> 549
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<210> 550
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 <212> DNA
 <213> Homo sapiens

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<400> 550
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<210> 551
 <211> 2805
 <212> DNA
 <213> Homo sapiens

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<400> 551
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<210> 552

<211> 625

<212> DNA

<213> Homo sapiens

<400> 552

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<210> 553

<211> 540

<212> DNA
<213> Homo sapiens

<400> 553

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<210> 554

<211> 860

<212> DNA

<213> Homo sapiens

<400> 554

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<210> 555

<211> 1318

<212> DNA

<213> Homo sapiens

<400> 555

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<210> 556

<211> 3054

<212> DNA

<213> Homo sapiens

<400> 556

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<210> 557

<211> 1088

<212> DNA

<213> Homo sapiens

<400> 557

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<210> 558

<211> 530

<212> DNA

<213> Homo sapiens

<400> 558

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<210> 559

<211> 1446

<212> DNA

<213> Homo sapiens

<400> 559

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<210> 560

<211> 469

<212> DNA

<213> Homo sapiens

<400> 560

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<210> 561

<211> 685

<212> DNA

<213> Homo sapiens

<400> 561

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taaaataaaa tacttctaata ggaac 685

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<210> 562

<211> 505

<212> DNA

<213> Homo sapiens

<400> 562

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<210> 563

<211> 1722

<212> DNA

<213> Homo sapiens

<400> 563

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<210> 564

<211> 1312

<212> DNA

<213> Homo sapiens

<400> 564

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<210> 565

<211> 1142

<212> DNA

<213> Homo sapiens

<400> 565

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<210> 566

<211> 1216

<212> DNA

<213> Homo sapiens

<400> 566

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<210> 567

<211> 1203

<212> DNA

<213> Homo sapiens

<400> 567

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<210> 568

<211> 1220

<212> DNA

<213> Homo sapiens

<400> 568

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<210> 569

<211> 2515

<212> DNA

<213> Homo sapiens

<400> 569

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<210> 570

<211> 1928

<212> DNA

<213> Homo sapiens

<400> 570

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<210> 571

<211> 1414

<212> DNA

<213> Homo sapiens

<400> 571

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<210> 572

<211> 1031

<212> DNA

<213> Homo sapiens

<400> 572

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<210> 573
 <211> 2069
 <212> DNA
 <213> Homo sapiens

<400> 573
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<210> 574
 <211> 1902
 <212> DNA
 <213> Homo sapiens

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<210> 575

<211> 1222

<212> DNA

<213> Homo sapiens

<400> 575

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<210> 576

<211> 1348

<212> DNA

<213> Homo sapiens

<400> 576

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<210> 577
 <211> 1055
 <212> DNA
 <213> Homo sapiens

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<400> 577
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<210> 578
 <211> 929
 <212> DNA
 <213> Homo sapiens

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<210> 579

<211> 1536

<212> DNA

<213> Homo sapiens

<400> 579

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<210> 580

<211> 1521

<212> DNA

<213> Homo sapiens

<400> 580

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<211> 969

<212> DNA

<213> Homo sapiens

<400> 581

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<210> 582

<211> 1241

<212> DNA

<213> Homo sapiens

<400> 582

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<210> 583

<211> 1496

<212> DNA

<213> Homo sapiens

<400> 583

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<210> 584

<211> 1657

<212> DNA

<213> Homo sapiens

<400> 584

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<211> 602

<212> DNA

<213> Homo sapiens

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<210> 586
 <211> 1271
 <212> DNA
 <213> Homo sapiens

<400> 586
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 <211> 935
 <212> DNA
 <213> Homo sapiens

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935

<210> 588

<211> 1456

<212> DNA

<213> Homo sapiens

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<211> 2111

<212> DNA

<213> Homo sapiens

<400> 589

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<211> 1379

<212> DNA

<213> Homo sapiens

<400> 590

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<212> DNA

<213> Homo sapiens

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<211> 3615

<212> DNA

<213> Homo sapiens

<400> 596

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<211> 1843

<212> DNA

<213> Homo sapiens

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<210> 598

<211> 1384

<212> DNA

<213> Homo sapiens

<400> 598

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1384

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<211> 1439

<212> DNA

<213> Homo sapiens

<400> 599

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<210> 600

<211> 1258

<212> DNA

<213> Homo sapiens

<400> 600

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<210> 601

<211> 2342

<212> DNA

<213> Homo sapiens

<400> 601

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 <212> DNA
 <213> Homo sapiens

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 <211> 361
 <212> DNA
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<210> 608
 <211> 760
 <212> DNA
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<400> 608
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<210> 609

<211> 476

<212> DNA

<213> Homo sapiens

<400> 609

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<210> 610

<211> 406

<212> DNA

<213> Homo sapiens

<400> 610

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<210> 611

<211> 433

<212> DNA

<213> Homo sapiens

<400> 611

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<210> 612

<211> 714

<212> DNA

<213> Homo sapiens

<400> 612

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cctgacctcg tgatecaccg gcctcggcct cccagggtgc tgggattacg ggcattgagc 120
accgcgccc gccggaactc tgtttcaaaa agaaaaaaa caaaggaaaa agagggtgtc 180
catgggcaat gaaggttggg ctacgtgcat accgtagggt ccagtgagt gctgccagt 240
gccatggttg gcttctgtt gctgtcaca gtctgggagg gagaagcagg cactcccatc 300
ctctctgtct ggtggttctg ggagcaccat agggacgccc aaggagggaa ggagcccac 360

```

```

tgcaccgccc cccaaccccg gccttccaga ctacgaaca gactcactcc cctcccggc 420
cctcatccac agagcgtgcc aggaagatgt cgagcccggg catcgacggc gaccccaagc 480
ctccatgctt gcctcgaaac ggtctgggtga agctgccggg ccagcccaac ggcctgggtg 540
cggccagcat caaccaagggc acgccagcca cctaagaacc gcccctgccg gccaccaccc 600
cccccacccc tcccaccacc cagcctgggt gctccactgt cccgggctgc cctgggtggg 660
ggcccggtgca ccccggcagg tggaccagcc tcagccttgg cacctgggca ccca 714

```

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<210> 613
<211> 531
<212> DNA
<213> Homo sapiens

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<400> 613
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gttctcagca ccgctcactg ctgccgggca cactgggacc agcaggctcc tcagcccaacc 120
ctgtccctcg gcccgccctt gccagagagg gacccagca catcggtggc acgggcaggg 180
ctcagccgct cccacctccc cacagaagcc caggagtgtg tggacgtctg agccagctt 240
tctgcgtgcc ctctggccc ctcactcccg gcagcgggccc ggctcggccc cactccccc 300
tccctaccgg gcaggggntt ccggggcctt ttcacctgga gaaacattcc cactccctt 360
tggcctccct gtactctgag ctgtgaatat ttttaacct gtaataacgg ccagctcttg 420
tgacacagag actattttat caattgtcag tcccgttcct ttaccatagg attctccaca 480
gtggcttccg actcaggctc caatggacca aataaaagcg ttttgttttg c 531

```

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<210> 614
<211> 907
<212> DNA
<213> Homo sapiens

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<400> 614
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cttctctttt atttattttg ttctccattt gtggccctca cctccgctcg ccttccctcc 180
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gttctgtgat ggtgcccag atgctgtggac tgagccaga ccgcaggctg cccgagcccg 420
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cgggctccag ccttttctcg ccggtgagcc ccgaggtcat gaagcggcg cgcgggggccc 720
tcacogagca gcgcgacatc atcaaggccc acgaggcgca caagatgcag agcaccccc 780
aggcccgcg caaggaatgg gagatggctc gcttcgggga ggcgggtgtc gccaggccag 840
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cggggca 907

```

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<210> 615
<211> 543
<212> DNA
<213> Homo sapiens

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<400> 615
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cagtccatgc caggccagag agtgggtcag ccgtctcagc tctttgagtg gttggtgctg 120
gtactggtct catggtttta gacctggcac ccagtgggta tggggagccc tgggcacctg 180
tgggcctact tatggaagtc atcctcttcc ctatcagggt accgcccaacc ctgtggtgca 240
gctgtgccc cagtttcccc ttgtgtccca ggtcccccact gtggcagttg ctcttctctg 300
agatccagcc agtgtagctg agtccctggg gtcttgctaa ctctctgcca gccctgaac 360
ccagaactct ctctttccct tggccactgg ctaggagcct ctaccactaa aaaaactcag 420
tttctagcc aggtgcagtg gctcacgect gtaacctcgg cactttggga ggcagggca 480
ggaggatcgc ttgagaacag gagtttgaga ccagcctggg caacatagtg agactccacc 540
tct 543

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<210> 616
 <211> 445
 <212> DNA
 <213> Homo sapiens

<400> 616
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 tctggcccc tatctcctga ccagctgagt catgaggccg gtttctctct ctctccact 180
 ttgtccccc agccaagctc taaagcaca gtaccgctg agacctgctg tttctgctgg 240
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 ctccaggttag acctggggcc ctggagctta ggggattctc cccacccag cccacacct 360
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 aaataaaaa caacatttt gcctg 445

<210> 617
 <211> 394
 <212> DNA
 <213> Homo sapiens

<400> 617
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 gcggcctgct ggacctgtac ctcatcgccg tcaccgacct gtactggtgc tcttgatcg 180
 ccactgacct ggtggtggtg gtgggctggg ccatcttctt cgccaagaac agccggggcc 240
 gtcggggcgg cgcagccagc ggcgcgcaca accaccacct gcaccaccac caegccgcgc 300
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 gcggggcgcc ggccgcneg gggcgccct gggg 394

<210> 618
 <211> 710
 <212> DNA
 <213> Homo sapiens

<400> 618
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 ccctgctgce cgggagcccc tccccggga gttcttgggt aagtccttcc cgggctctct 180
 tgtgtttttg cctcattcct actgtcacac aggtcacgag ggtggactcc ctacaatcaa 240
 caaagcaaac agagagcctg tgggaggggc tgacagcagc agccggctgt ttgggggatg 300
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 gagatgatgg atgacagct ggattttcgt gatgaaggac ggaagcagca gcggcccgcc 420
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 tgggggtggc ccactgccct cccctggccc tcatgtcccc ccggggctgg ggtccgctg 660
 cctgtgctgt gcttgccagc tgcataata aaccaccatg gcctgagggc 710

<210> 619
 <211> 557
 <212> DNA
 <213> Homo sapiens

<400> 619
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 tatgtgccct gcagtcatac aggagtgga gaagagggc ggacagccct ggcagctcat 180
 cgagccctg gatggattcc accccaacga ggtaagtcac gtcacatggt ggtgcagaa 240
 ggctatttga tggtttgggt gtttttaatt atggttacac attcatgtgt ttatttttat 300
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 aataaaaaa aagtgaatt tgggacaata gggaaataaa gttagaatta taccctggatt 420
 cctgattnaa tttctataat tcataaaata tgtgcagggc attcctgaga aactgccaga 480
 agggcagctc tgtgcagatc taaaaggggc agtaagccat ggcttcata atacaagaaa 540

aataaatcaa gcactcc

557

<210> 620

<211> 728

<212> DNA

<213> Homo sapiens

<400> 620

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tttaccacct tcaccttcca gggacgcagt tgttttgagg tttagcgtgg cagctctgtg 660
cagtgtttga gcctacagtg ggatacatag ggtcaaattg agaataataa actgagtcac 720
tctcctag 728

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<210> 621

<211> 753

<212> DNA

<213> Homo sapiens

<400> 621

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gaggtccatt tcatttcaat gagtgtgaca gccgctcttc ttggggccta tgggggaaag 120
gcatttggtc gtggtgggag tgaagctgct cccacaagat gcattcccaa ctggatcagg 180
aagaccttca gatttagggg aggtctttgt ggaagtcttt agtggagtct tccctgccc 240
gctagatgtc cgttcggttt tagcccgctg tggctactgg atggtccgct gtgcgggctt 300
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ggtcctccag ggaagcgcgg tgcctcctc ttgcctcgcg cgtcccgggt ttctcctggg 660
cttgggaacc ttccagacc tgaagtagcc ggcggcgtcg ctgcccgtga cccggaggag 720
cgtggccttg gcctgcccc tgggcgcttc gtg 753

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<210> 622

<211> 685

<212> DNA

<213> Homo sapiens

<400> 622

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gctcgtgtgt cccccaggca gatctgggca ctttcccaac ccaggtttat gcgtctccag 180
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cacttaagga gactctaatt aaagctgatg aattttcttt tctgtccaaa caagtaaaat 660
aaaaataaaa gtctatttag atgtc 685

```

<210> 623

<211> 596

<212> DNA

<213> Homo sapiens

<400> 623

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ctccatccct gttgtccgga gccagctcac tgtcttccac actggtgcta actggcccag 60
gcactggagt ggaatagaat gcagctggag gctacgcatg gcctctgcag cacacgcagc 120
tggagagggc ttctgtccct gtcagcggca gagggcggtg gggctggccg gggcaccttg 180
tccttgctat ggtccacatg ctacgctgt ccacctgcca ggtggagtgt atgtggctgt 240
ggccctccct cgtggaggtg ccgtgcttta aagaggcctt agtggccggg atgggcacag 300
tgttttgaag ggaggtggga gctcttgctc tcctggtcac tgcagaatga cagagaaggt 360
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ctaaagatgt gcttctcccg tgtctgtcat aactgagac caacaggeta cagtgtccct 480
gattcttgga aaagcctgga gaagctgggg agatgcggtt cacaatgcct cggatatagga 540
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<210> 624

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<400> 624

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gaattcggcc aaagaggcct a 21

```

<210> 625

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<400> 625

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gaattcggcc ttcattgcct a 21

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<210> 626

<211> 8

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<220>

<221> unsure

<222> (7)..(8)

<400> 626

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gaattcnn 8

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<210> 627

<211> 15

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<220>

<221> unsure

<222> (1)..(9)

<400> 627

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15

<210> 628

<211> 15

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<220>

<221> unsure

<222> (1)..(9)

<400> 628

nnnnnnnnng tcgac

15

<210> 629

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> linker sequence

<400> 629

acggcctctt tggcctcga gaca

24